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OCCUPATION, TUBERCULOSIS AND COMPENSATION LAWS[1]

LEOPOLD BRAHDY[2]

There is no state or federal law declaring tuberculosis to be an occupational disease. Nevertheless, tuberculosis, as an occupational disease, has become a serious problem in sanatorium administration, in medical care of patients, in rehabilitation of former patients, in employment of persons with X-ray abnormalities of the lungs, in prevention of the disease and in the just administration of workmen's compensation. In claims of hospital employees for compensation for tuberculosis, specialists have testified that it was of occupational origin. Compensation boards have merely rephrased in their legal decisions the testimony given by specialists, and thus this problem has arisen. In some cases the disease is, in fact, occupational. Here the decisions of compensation boards based on the medical testimony have been correct and the duty of the medical profession has been well done. Other cases which, in fact, are not occupational, also have been classified as occupational by compensation boards. The decisions have been erroneous because they were based on erroneous medical testimony. The responsibility for these decisions rests on the medical profession. Ours is the blame for any harm resulting from these errors and ours the duty to correct them.

COMPENSATION LAWS

To charge to the employer the major part of the financial burden of injuries and diseases which arise out of an occupation is the chief objective of a workmen's compensation law. The provision of sick-pay and medical care for occupational diseases constitutes a great social achievement and is an important factor in preventive medicine and community health.

The District of Columbia and every state, with the exception of Mississippi, have compensation laws giving certain employees some income and some medical care for accidental *injuries* sustained by reason of their

[1] Presented before the Medical Section at the 37th annual meeting of the National Tuberculosis Association, San Antonio, Texas, May 6, 1941.

[2] 230 East 71st Street, New York City.

occupation. In some states the law also contains a list or "schedule" specifying certain occupational diseases for which compensation must be paid. Tuberculosis is not listed in the "schedule" of any of these state laws. Some states have "blanket coverage" of occupational disease.[3] In general terms "blanket coverage" means that instead of a limited list or "schedule" of occupational diseases the law states that *any* disease is compensable if, in the individual case, it was due to the particular occupation.

DECISIONS ON OCCUPATION AND DISEASE

Erroneous decisions on the occupational origin of any disease have serious consequences for medical practice. If to-day we were ignorant of the relationship of silica dust to silicosis (as we were a few decades ago) many hundreds of miners would be deprived of compensation. Furthermore, thousands of miners and stone-cutters would have silicosis if they had not been protected by the measures based on our knowledge of this aetiological relationship.

Let me give you a hypothetical case. Assume a stone-cutter changes his occupation and works as a porter in a hotel for a year; at the end of the year he is disabled because of silicosis and claims compensation; assume that a physician testified that the dusty porter work of the past year either activated or aggravated the disease and the the history of the man's occupation as a stone-cutter during the preceding ten years is not the determining factor in the disease and, consequently, that the employing hotel is held liable for the compensation on that testimony, and that therefore the stone-cutting company is released from liability. The decision would be unjust. Its consequences would extend beyond the important field of administration of justice into the field of medicine and public health.

[3] The compensation laws of the District of Columbia and of eight states (California, Connecticut, Illinois, Indiana, New York, North Dakota, Ohio and Wisconsin) have "blanket coverage." In Massachusetts, by judicial interpretation, an injury includes the infection of a communicable disease. As far as tuberculosis is concerned, this interpretation is the equivalent of "blanket coverage." We are, therefore, at present concerned with the laws of these ten jurisdictions. Tuberculosis in hospital personnel cannot be compensable elsewhere without legislative change in the law (which is likely in some states) or judicial constructions of "injury" as including communicable diseases. Such judicial construction is possible only in those states that have not specifically *excluded* occupational diseases. In Connecticut no hospital employee with tuberculosis has carried a claim to the court of last resort. In the nine other jurisdictions mentioned, tuberculosis in a hospital employee exposed to the disease has been classified as being occupational in origin and, therefore, as coming within the compensation law.

The probable effects of such a decision are: (*1*) preventive measures in silicosis are scuttled where such testimony is given official endorsement; (*2*) rehabilitation of men with silicosis is made doubly difficult if the next employer risks being held liable for the disease; (*3*) a physician who advises a stone-cutter with early silicosis to take a job as porter would be giving advice contrary to an officially accepted medical doctrine that such work is harmful for a silicotic. The result is that physicians not specially trained in occupational diseases soon accept this legal fiction as scientifically established. To paraphrase Gresham's monetary law, bad medical doctrine with official imprint drives out good scientific fact.

Physicians, therefore, have a direct professional concern in decisions concerning compensation for occupational diseases.

Certain communicable diseases among hospital personnel are clearly of occupational origin. There is seldom doubt of the occupational origin of measles in a nurse who had contact with the disease in the hospital. Of course, there is the remote possibility that some one nurse may have acquired her infection, as other adults may, from a disease carrier in a public place or from a child in her own home. However, when the probabilities are so great that she acquired it in the course of her occupational duties, when there is no way of distinguishing the rare case that was acquired outside the hospital, we can classify nearly all cases of measles, scarlet fever, diphtheria, typhoid fever and chicken-pox as occupational when occurring in any one who, in course of duty, had recent contact with the disease. Although the occupational origin is certain, this was not established by law or by rules of any state compensation commission. In every case in which it has been decided that the disease was occupational, a physician's certificate is on file stating that in this particular case the disease was due to occupation. Signing such a certificate is simple. No one questions the conclusions stated in the certificate and the doctor never hears again of the aetiological relationship of the disease to occupation. The very simplicity of the procedure causes many physicians to lose sight of the fact that the decision rests on that certificate. It constitutes the medical testimony establishing the basis for the decision. No compensation board or court could award compensation without such testimony. All decisions of compensation boards are based on medical testimony of the aetiological relationship of the disease to the occupation in each individual case.

Yet such diseases under some conditions may not be occupational. For example, an interne was taken ill with typhoid fever two days after re-

turning from a month's vacation at home. On the basis of our knowledge of the incubation period we can classify the disease, in this case, as not occupational.

There are other cases in which the classification is more difficult. If there are differences of opinion among physicians, two contradictory medical certificates may be submitted to the compensation board. Hearings are then held and the two physicians state the basis for their divergent opinions. Other specialists and consultants may be called to state their views. Physicians have maintained that only physicians should decide these problems and they usually have met these self-imposed responsibilities for the decisions on medical questions.

OCCUPATION AND TUBERCULOSIS

On enrollment, many student nurses have no roentgenographic evidence of tuberculosis and have negative tuberculin reactions. If any of these students later present signs of tuberculosis, the probability is that they acquired that infection in the course of their employment. There is no doubt that a few of these young women acquired the infection in the same way as students in academic schools who have no occupational contact with patients. Nevertheless, the probability that the disease developing in a previously tuberculin-negative nurse was acquired in the course of her duties is strong and there is no way of differentiating the few infections that were acquired otherwise. In a claim for compensation in such a case, a physician's certificate is submitted stating that the disease is probably due to occupation. Nothing further is ever heard on the question of occupational origin because there is general agreement on the subject. There being no difference of medical opinion, such a case is classified by compensation boards as occupational, on the basis of the medical testimony represented by the one physician's certificate.

There are other cases that are clearly not acquired or activated by reason of occupation in the institution in which the patient was employed when the disease was discovered. In many such cases, however, the claim is supported by a specialist's testimony.

Four examples from New York State will illustrate.

CASE REPORTS

Case 1: E, a colored nurse, graduated from a nurses training school in 1930. For a year she did private nursing, until October, 1931. She then had an X-ray film taken because of pain in her chest. This showed tuberculosis.

She was treated at a sanatorium and at home from 1931 to 1935. In 1935, she applied for employment at another sanatorium. X-ray films showed the lesion in the right upper lobe apparently healed. There were a few râles and harsh breathing in the right upper lung; otherwise the examination was negative.

The sanatorium gave her a job as ward nurse on condition that she rest during her hours off duty. This condition she faithfully observed. She remained in good health for five years until 1940, when a routine X-ray film showed an extension of the lesion due to additional infiltration. Physical signs were unchanged. There were no symptoms.

A specialist testified that "she suffered reactivation in the same area where she showed a lesion before employment in 1935. We are dealing with a reactivation. In the absence of any known cause it is my opinion it was the exposure to tubercle bacilli in her work during the past five years that caused the reactivation."

On the basis of this testimony the employing hospital was held liable for compensation and the cost of all medical care.

Case 2: V, a graduate nurse, age twenty-five, was first employed at a hospital in November, 1938. She had never had any previous illness nor any previous X-ray films. On employment the X-ray film showed a sharply circumscribed area of increased density just above the left second anterior rib. Sixteen months later (March, 1939) a small area of infiltration was found extending from this density. The compensation board ruled on the basis of the medical testimony that the "exposure to tuberculosis since November, 1938 was a competent producing cause of her disability." The employing hospital was held liable for all compensation and medical care.

Case 3: S, a graduate nurse, trained at another institution. In 1934, at the age of twenty-four, she applied for a position in this hospital. The X-ray film showed a fairly dense lesion in the first intercostal space. There were no symptoms and no physical signs and the examination was otherwise negative. The lesion was apparently healed. She was permitted to work with periodic X-ray examinations. These examinations showed steady clearing; in January, 1936, the lesion was hardly visible. In May, 1936, it had disappeared, but there was a new area of infiltration about one and one-half inches below the site of the lesion seen in 1934. The sputum examination was now positive.

A tuberculosis specialist testified he could not see any aetiological relationship between the old and the new lesion; that it was probable that the new lesion was due to a new exogenous infection as a result of her occupation. On the basis of this testimony the hospital was held liable for compensation and medical care.

Case 4: E was a fifty-two year old hospital porter; he was hired in 1935 at the age of forty-nine. In 1907 he had had tuberculous osteomyelitis of the ribs. A preëmployment X-ray film showed a 3 cm. rounded, well circumscribed lesion in the left second interspace. There were old fibroid changes in both apices. The diagnosis was healed tuberculous focus.

He was permitted to work with periodic examinations. These showed no change until November, 1938, when he developed an acute lesion in the upper lobe of the opposite (right) side. Two specialists testified that the lesion in the right lung was probably due to a new infection acquired by reason of his occupation during the last five years. On the basis of this testimony the employing hospital was held liable for payments of compensation and all medical care.

In all these cases the employing institution had specialists testify that the disease and the occupation were not related. The employer, however, is handicapped because specialists are reluctant to testify that a specific case is not occupational. The specialist knows that the employee is facing a long illness and that without compensation benefits he will probably have financial worries in addition to the physical burden of the illness. When the employee is a younger colleague or a nurse it is understandable that many specialists prefer not to testify against the claim.

No physician wants an employer held liable when, in fact, the disease is not occupational or due to some previous employment. Yet, many evade the responsibility of testifying with the conscience-soothing thought that someone else can do it. They evade testifying, perhaps because they do not realize the disastrous effects on rehabilitation, on preventive medicine and the other serious consequences that result from erroneous testimony and resulting erroneous decisions. It must be stated that there are a few notable and praiseworthy exceptions to this evasion of responsibility. They are too few to overcome such testimony as in the four examples given.

Is it true that recurrence may be due to new exposure? If so, the hospital or sanatorium should not employ ex-patients. Opportunity must be found for them in other occupations. Hospitals must refuse to place them in jeopardy even if the individual is willing to assume the risk. Hospitals do not hire men recovered from cardiac decompensation to heave ash cans, even where there is no liability for the recurrence of cardiac decompensation. Why not? Because it is known the work places the men in danger.

For decades, hospitals and sanatoria have rehabilitated discharged tu-

berculosis patients by employing them. These institutions desire to continue that important phase of their work. Do they, thus, knowingly place ex-patients in danger of recurrence? Do we really believe there is any hazard of exogenous reinfection or activation of arrested lesions by exposure to tubercle bacilli? If there is any such hazard for the employee, then there is even more hazard for the convalescent patient. If there is such a hazard, patients would have much less chance of recovery in a sanatorium than in their own homes. In a sanatorium most patients would be reinfected even though there is sanitary control.

These decisions discourage preventive medicine. Obviously the precautions against infection inside an institution will not diminish the cases of nonoccupational tuberculosis which will arise among the employees. If these are all improperly classified as occupational, there is no standard by which a hospital can judge the efficiency of its own preventive measures. Seemingly the best preventive measures will be nearly useless, for many cases in a hospital will continue to occur because of the fact that they are unrelated to occupation in that hospital. The duty of the hospital is to discover these cases as early as possible. An institution which conscientiously searches for early manifestations among those employees who were already infected when they began their work may, because of this case-finding, have the highest recorded morbidity even though it has completely eradicated occupational tuberculosis. Thus, the occupation in institutions interested in tuberculosis prevention is falsely stigmatized as harzardous because of the early diagnosis campaigns among its own personnel. Under these conditions, prevention of occupational tuberculosis cannot progress. It must be mentioned here that the negligent general hospital with the false statistical low morbidity is not only neglecting its employees' health but placing some of its patients in danger of infection by not uncovering tuberculosis among employees.

To refuse employment to anyone whose chest X-ray film shows the least suspicion of a lesion is an effective way of decreasing tuberculosis among hospital employees. Though most of those rejected will never develop any disease, the rejection by one institution will make it difficult for them to obtain jobs elsewhere. The psychological result of rejection for "suspicious spots" is well known. This procedure does no one any good, but it protects the hospital from unwarranted claims. Of course the proper procedure, which is socially desirable and medically sound, is to employ these people and keep them under observation. There is no better place for such people to work than a hospital where facilities for

periodic examinations are always available. But what hospital administrator will employ them if a few years later he may be accused of having caused reactivation by employing these people in the hospital?

Another serious aspect of the officially accepted testimony, as cited in the 4 cases, is that some nurses are deprived of the benefits of the Workmen's Compensation Law to which they are entitled. Assume that a girl who is tuberculin-negative when she enrolls becomes infected in the last months of training. After graduation she practices her profession on private duty until, years later, she is found to have a lung lesion. In cases, such as the 4 that have been cited, the testimony was that recent exposure is the probable cause of any discovered tuberculosis. If its decisions are to be consistent, a compensation board could not award her any compensation against the hospital in which she trained years prior to the clinical manifestation of the disease. The legal fiction of recent infection as a cause obscures the fact that she probably acquired the infection in that hospital.

PROPOSAL TO LEGALIZE WAIVERS OF COMPENSATION

The failure of the medical profession to establish definite criteria for occupational tuberculosis is chiefly responsible for erroneous compensation decisions. Some specialists, realizing that these decisions place financial burdens on institutions when the burden actually belongs elsewhere and that they hamper medical and social efforts in tuberculosis, have sought legislative action as a solution. They propose that employees sign waivers that they will not claim compensation for tuberculosis. At present, such waivers are illegal in most states and would require legislative amendment of the workmen's compensation laws. It is important to note that inherent in the waiver is the admission that the applicant for employment is more likely to get the disease than he would be in other occupations.

For what type of case do they propose this limitation of the compensation law? Some cases of tuberculosis are clearly of occupational origin. The compensation law is here a most beneficent stimulus to the study and use of methods of prevention. But the infection of employees is not preventable at present in *all* cases; some employees will become ill in line of duty. These few bear the personal burdens, the long invalidism, the altered lives and blighted hopes. There is no reason in law, in ethics or in practice, why a hospital should not bear the major part of the financial burden of such illness acquired in course of duty. No employer, least of

all a hospital, should seek to be exempted (by use of waivers or otherwise) from providing medical care and sick-pay. On the contrary, where compensation acts do not cover true occupational tuberculosis, hospitals should voluntarily assume this obligation to their employees when tuberculosis results from employment in the hospital.

Waivers have been advocated for those seeking employment after having recovered from tuberculosis. The purpose of the proposed waiver in such cases is to exempt the new employer from liability in case of recurrence. There is seemingly some justification for waivers when ex-patients apply for employment in a hospital or sanatorium. Those who advocate the use of waivers rightly say, "Even though we ourselves do not believe that the employment causes recurrence, hospitals and sanatoria have been held liable on the basis of that allegation." Many cases to support this contention can be quoted, but the four examples previously cited are sufficient. Let us bear in mind that no compensation law creates any new liability unless the recurrence is due to the new occupation. If the disease was originally occupational the liability for such a recurrence reverts to the original employer. If the recurrence is not due to the new occupation and was not due to previous employment, there is no liability on anyone's part. In any individual case, therefore, the decision is not a legal but a medical question.

If the decision in the cases that have been cited is not in accord with the medical consensus, then doctors have been remiss in permitting the theories of a small minority to become the basis of compensation decisions. These decisions are not in the law; they are not in the judicial interpretation of the law; they are based solely on the testimony of medical men who qualify as experts. How shall we meet this situation?

We cannot evade the problem by asking legislatures to accept the minority opinion that recurrence or activation of tuberculosis is occupational. On the other hand if you tell the legislature there is no hazard then you are saying there is no right to compensation. If there is no right, the legislature should not legalize a waiver of a nonexistent right. Legalizing waivers means putting the stamp of legislative action on the assumption that we knowingly place discharged patients in jeopardy when we employ them. It implies that a sanatorium is a dangerous place for a patient whose tuberculosis has become arrested.

To have the legislature sanction waivers is to created a new liability—this one being more serious, namely, malpractice. For example, you keep Mr. Jones, a private patient with recently arrested tuberculosis, in

the sanatorium under observation until you are certain that there is no recurrence. Your fears are justified and he does have a recurrence. Assume you have asked the legislature to permit waivers or exemption of the hazard of reinfecting an employee with arrested tuberculosis. What can one then say if Mr. Jones alleges that he was reinfected because he stayed in the sanatorium as a patient and the record shows that physicians have asserted that there is such a hazard? If waivers have been legalized then the legislature has, by implication, established this allegation of a hazard to be a fact.

SOLUTION OF THE PROBLEM

The solution of the problem is not in exemptions or waivers or in any other legislative or judicial action. The compensation law has placed the remedy in the hands of specialists in tuberculosis. It is not the law that is at fault, but the testimony of a few physicians. It is the duty of specialists individually and also acting collectively in medical societies to formulate the criteria by which compensation boards may be guided. It is the specialist's duty to state the facts and to repeat them and to shout them from the housetops until compensation boards acknowledge their validity. We must popularize among practitioners and laymen the principles of occupational tuberculosis, just as we have popularized the knowledge of methods of diagnosis and treatment.

To allow the bizarre epidemiologic vagaries to stand unchallenged will eventually involve us in more and greater difficulties. They will impede and they may nullify progress in the prevention of such tuberculosis as is of occupational origin. They already hamper rehabilitation. They interfere with hospital administration. They obscure the scientific data on which action depends.

The medical profession must not permit the legal fiction that tuberculosis is due to the occupation at the time the disease happens to be discovered, when we know that, with the exception of student nurses, very few cases are related to that occupation. This is completely within the profession's province and powers. It is imperative that at the same time the profession advocate that whenever tuberculosis is, in fact, occupational in origin, the patient shall receive medical care and sick-pay from the institution in which the injurious exposure occurred. All the aspects of this compensation problem are automatically solved when the known facts as to pathogenesis are presented by physicians clearly enough and often enough to be accepted by compensation boards.

Addendum: In April, 1941, Minnesota enacted a law giving limited medical care and sick-pay to employees of State hospitals who acquire tuberculosis by reason of contact with patients. The law requires new employees to undergo physical and X-ray examination and "such additional special diagnostic tests for the detection of the presence of tuberculosis as" shall be required. Only those certified to be free of tuberculosis will be employed.

Minnesota physicians may find such certification in many cases far more difficult than the Legislature imagined.

SUMMARY

1. There is no law that tuberculosis is an occupational disease.

2. The testimony of a few physicians has caused tuberculosis to be classified as an occupational disease in hospital employees regardless of known infection or disease existing prior to employment.

3. Such erroneous testimony hampers prevention, hospital administration, rehabilitation and progress in other fields. This testimony deprives some nurses of the benefits which the compensation law should give them.

4. The responsibility belongs to the medical profession and no one else can solve the problem.

SUMARIO

1. En Estados Unidos no existe ninguna ley que declare que la tuberculosis es una enfermedad industrial.

2. El testimonio de algunos médicos ha hecho clasificar la tuberculosis como enfermedad industrial en los empleados de ciertos hospitales, haciendo caso omiso de si había o no antes del empleo infección o enfermedad tuberculosa conocida.

3. Todo testimonio erróneo de este género obstaculiza la profilaxia, la administración de los hospitales, la rehabilitación y hasta el adelanto en otros campos, a la vez que priva a algunas enfermeras de los beneficios a que tendrían derecho conforme a las leyes de indemnización.

4. La profesión médica tiene la responsibilidad y no otra puede resolver el problema.

THE TOLL OF TUBERCULOSIS IN THE INFECTED PART OF THE POPULATION

JULIUS HOLLÓ[1]

A simple measure of the toll of tuberculosis in the infected part of the population may be found in the *annual fatality rate* of tuberculosis. This is the annual mortality rate of tuberculosis divided by the incidence of tuberculous infections in the population of the same year n . In a group in which every member is infected, the annual fatality rate is equal to the annual mortality rate, as it may practically be the case in some older groups, say over sixty years of age, of certain urban populations. In other groups, in which only one-tenth or one-twentieth of the members is infected, as it is the case in groups of young children, the annual fatality rate is ten or twenty times higher than the annual mortality rate. It is obvious from these examples that, for certain purposes, the annual mortality rate has to be replaced by the annual fatality rate, even at the cost of some inexactitude, involved in the determination or estimation of the incidence of infections in the investigated groups.

Whitney and McCaffrey (1), on the basis of large scale tuberculin tests performed in 1934–1936, have found that 50 per cent of the whole population reacted to tuberculin.[2] Accepting the assumption that the number of positive reactors is practically identical with the number of actual tuberculous infections, we may put the incidence of actual tuberculous infections among the population of the United States to 50 per cent in 1935. The annual mortality rate from tuberculosis was 5.5 per 10,000 in this year, and so the annual fatality rate of tuberculosis in the United States during the year 1935 can be computed to have been $\frac{5.5}{0.5} = 11$ per 10,000. About one of every thousand infected has died from tuberculosis in this year.

[1] 141 East 88th Street, New York, New York.

[2] The exact numbers are: 46.5 per cent for the white, 47.8 per cent for the colored and 47 per cent for the whole population. Since only 75 per cent of the first negative reactors were retested with second strength of PPD, and since the computation of the percentages was done on the basis of the age distribution of 1930 when the population was somewhat younger than in 1934–1936, these numbers must be considered as somewhat low.

For previous years this computation cannot be performed with a similar exactitude, since we do not have reliable figures for the incidence of positive reactors among previous populations of the United States. And yet the incidence of positive reactors in previous populations can be estimated with an exactitude which is sufficient to show that the annual fatality rate of tuberculosis has considerably dropped during the last decades.

First of all, we can make two obvious statements: (*1*) the incidence of tuberculous infections in the United States has definitely diminished during the last decades; and (*2*) it was never as high as 100 per cent. It is very doubtful whether it ever could have been even as high as 80 per cent, since the proportion of younger age groups in the population was higher previously than it is now.

In 1900, 44.3 per cent of the population of the United States was below twenty years of age (2). Even an incidence of 60 per cent positive reactors in this age group and one of 100 per cent in the age group above twenty years would give only $44 \times 0.6 + 56 \times 1.0 = 82$ per cent positive reactors in the whole population, and I suppose that everyone will agree that the estimates of 60 per cent and 100 per cent are exaggerated, especially for a country in which a great part of the population has lived in rural districts. We can, therefore, state with a high degree of probability that the incidence of tuberculosis in 1900 in the whole population of the United States was maximally 80 per cent. Since the annual mortality rate of tuberculosis was 20.2 in this year, the annual fatality year of tuberculosis in 1900 can be computed to have been at least $\frac{20.2}{3.8} =$ 25.2 per 10,000 infected. This number is 2.3 times greater than the annual fatality rate of tuberculosis in 1935. From 1900 to 1935 the incidence of positive reactors has declined from maximally 80 per cent to 50 per cent, that is, maximally 1.6 times; that means that the diminution of the annual mortality rate of tuberculosis from 20.2 to 5.5 during this period, which is 3.7 times, was mainly due to the corresponding diminution of the annual fatality rate of tuberculosis.

The same can be stated for a shorter part of this period. In 1915, twenty years before 1935, the annual mortality rate of tuberculosis was 14.6. As to the incidence of reactors in this year, we can make the following estimate: from the 127 million inhabitants of the United States in 1935, 64 per cent or 81 million were older than twenty years of age (2). Subtracting from this number 4.5 million, that is, the approximate

number of those who lived in the United States in 1935 but came to this country after 1915, we get 76.5 million.[3] This is the number of those inhabitants of 1935 who were already living in this country in 1915. These 76.5 million——77 per cent of the population of 1915, which was then 99.3 million——had 60 per cent reactors in 1935, this being the percentage of reactors found by Whitney and McCaffrey (1) in the age group over twenty years of age in 1934–1936. Even if we assume that the percentage of reactors had not increased in the same group of persons during twenty years of their lives and that 100 per cent of those members of the population of 1915 who died up to 1935 were reactors in 1915, we get only $77 \times 0.6 + 23 \times 1.0 = 69$ per cent reactors for the whole population of 1915 as a maximum number. Using this number we get $\frac{14.6}{0.69} = 21.2$ as the *minimal* possible number for the fatality rate of tuberculosis in 1915. We see again: the bulk of the drop of the annual mortality rate of tuberculosis from 14.6 in 1915 to 5.5 in 1935 was due to the corresponding drop in the annual fatality rate during this period.

In this connection it may be of some interest to note the following point, which we want only to mention at this occasion. All evidences, theoretical as well as empirical, show that the diminution of the incidence of reactors in the last decades is the more pronounced the younger the compared age groups. In older age groups the diminution is almost negligible, the incidence of reactors in these age groups being even to-day not very far from the maximum possible value of 100 per cent. The diminution of the annual tuberculosis mortality rate in the older age groups is therefore practically equal to the diminution of the annual tuberculosis fatality rate in these age groups, whereas in the younger age groups the diminution of the mortality rate is very much influenced by the corresponding remarkable drop in the incidence of tuberculous infections in these age groups. That is probably the chief cause of the fact that the diminution of the mortality rate of tuberculosis is much greater in the younger than in the older age groups. For illustration we have tabulated some ratios of the annual tuberculosis mortality rates of 1910 and 1935 for different age groups:[4]

[3] Of the inhabitants living in the United States in 1935, 3.45 million came as immigrants from 1915 to 1930 (3). Adding one million for 1930–1935, and assuming for simplicity that all of them were over twenty years of age, we get 4.5 million.

[4] The calculations are made from the data of Wolff (4).

Age Group	Tuberculosis mortality rate in 1910 / Tuberculosis mortality rate in 1935
0–1	10.0
5–14	4.9
35–44	3.5
55 and over	2.3

The number 2.3 is very close to the numbers we found for the diminution of the annual fatality rate of tuberculosis of the whole population during this period.

The annual fatality rate of tuberculous infections in the year n must be definitely distinguished from *fatality of tuberculous infections of the year n*, which we define as the proportion of individuals, becoming infected during the year n, that will ultimately die from this disease. Before attempting to make a computation of this number, we have to make some preliminary remarks:

It was simple to relate the number of annual tuberculous deaths to the number of the infected only, instead of relating it to the number of the whole population. It is somewhat less obvious how to make a similar transformation of another usual statistical measure of the toll of tuberculosis, which also is related to the whole population group, not only to the infected part of it. We are thinking of the statistical notion "chance of a member of a population group of eventually dying from tuberculosis."

Chance is synonymous with probability, and every statement about it has therefore the form of a prediction. In statistics this prediction is made on the ground of the deliberate assumption that the statistical data from which this chance was computed, and which in our case are the annual mortality rates from tuberculosis and the annual mortality rates from all other causes in all the age groups of the actual population of the year n, shall remain unchanged in the future to which the prediction belongs. We know however that this assumption is not valid, and so the chance of eventually dying from tuberculosis is related to a constructed future and contains no real prediction at all. Neither is it based on the actual watching of 10,000 or 100,000 persons from birth to death, an experience which would be obsolete before it was completed, but is computed solely from statistical data of the calendar year n. It is therefore a projection into the future of the statistical evidences of, and only of this one year n.

In order to make this projection more tangible, it is customary to

relate it to the so-called stationary or life table population of the year n. This constructed population is defined as follows: (*1*) it is derived from a successive series of newborns of equal annual number, (*2*) all of its age groups show the same statistical behavior as the corresponding age groups of the actual population of the year n. Past, present and future of life table populations are identical; statistical chances have, therefore, the meaning of real probabilities, that is, predictions, in such populations. Actual and life table populations of the year n differ from each other—besides their future—only as to their age distribution. The difference is due to the fact that the statistical behavior of the actual population was not the same in the past as in the year n.

We will now try to give a formula for the chance of a freshly infected member of the *life table population* of the year n of eventually dying from tuberculosis, emphasizing again that in vital statistics every chance of eventually dying is related to life table populations. We have chosen a freshly infected member instead of any infected one, because we want to take in account all the tuberculous deaths that occur during the whole course of the tuberculous infections. We are doing this not only because of technical advantages, but because in life table populations the chance of a freshly infected person of eventually dying from tuberculosis is identical with the fatality of tuberculous infections, as defined above.

It is clear that for a member of the cohort of the newborns of the year n, of which no one is yet infected with tuberculosis, the chance of eventually dying from tuberculosis is the product of two probabilities:

Chance of the newborn of the year n of eventually dying from tuberculosis = chance of this newborn of becoming eventually infected with tuberculosis × chance of the freshly infected of eventually dying from tuberculosis.

It follows from the definition of the life table population of the year n that in it the age distribution, infection rates and the annual fatality rates of tuberculosis, in all different age groups, will remain the same in the future as they were in the year n. In a life table population the chance of a newborn of eventually becoming infected with tuberculosis is therefore equal to the attack-incidence of tuberculous infections[5] among the dead of this population, and the chance of eventually dying from tuberculosis of any freshly infected member of the cohort of the year n is

[5] Attack-incidence of tuberculous infections in a community is defined as the percentage of the population that has at some time been infected with tuberculosis (Hart (5)).

equal to the same chance of any person freshly infected in the calendar year n. Making the substitutions which these equalities allow us, and also substituting, *per definitionem*, chance of the freshly infected of the year n of eventually dying from tuberculosis with fatality of tuberculous infections of (acquired in) the year n, we get, after transformation the following equation:

Fatality of tuberculous infections of the year n =

$$\frac{\text{Chance of the newborn of the year n of eventually dying from tuberculosis}}{\text{Attack-incidence of tuberculosis infections among the dead of the life table population of the year n}}$$

In this equation the fatality of tuberculous infections of the year n is derived solely from statistical evidences of the actual population of the year n, and is independent of the accidental age distribution of this population. It is, therefore, a correct measure of the fatality of tuberculous infections under the statistical conditions of the actual population of the calendar year n, and is standardized to the age distribution of the life table population of this year. It should be called chance of the freshly infected of the year n of eventually dying from tuberculosis, standardized to the age distribution of the life table population of the year n. We prefer to replace this long denomination with the shorter "expected fatality of tuberculous infections of the year n."

Practical applications of the formula: Actual figures for the numerator of our formula, that is, for the chance of newborns of different calendar years of eventually dying from tuberculosis, can be computed in the usual way. Chances being related to life table populations, it is clear that they cannot be computed by simply dividing the number of annual tuberculosis deaths with the number of deaths from all causes in the actual population. The results so obtained would be distorted, due to differences in the age distribution of the actual and of the life table population. Dublin and Lotka (2) have given an example for the amount of this distortion. In 1930, the chance of eventually dying from tuberculosis for a person aged ten was for males 4.5 per cent and for females 3.6 per cent. The ratio however of tuberculosis deaths to all deaths over ten years of age was in the same year 6.1 per cent for males and 5.9 per cent for females, which is a considerable difference. The correct computation is done by summing up the deaths from tuberculosis in all age groups of the life table cohort, and by dividing this sum with the sum from all deaths

in the same range of ages. A few data so obtained are published in the August, 1939 issue of the Statistical Bulletin (6):

Chance of the newborn of eventually dying from tuberculosis in the United States

1920	1937
White females, 5.8%	White females, 2.5%
White males, 6.5%	White males, 3.5%
	Colored females, 7.0%
	Colored males, 8.2%

Figures for the denominator of our equation, that is, for the attack-incidence of tuberculous infections among the dead of life table populations, could be computed from the attack-incidences of tuberculous infections among the dead of all the different age groups of the actual populations and from the age distribution of the dead of the same life table populations. Since at present we do not know the attack-incidences of tuberculous infections among the dead of different age groups of any actual population, these figures cannot be exactly computed. But they can be estimated with an accuracy which is, we believe, sufficient to answer some practical questions.

The following table shows the differences in the age distribution of the living and of the dead of the year 1937.

Living of 1937,* percentages			Dead of 1937 (7) percentages		
0–19	35.0		14.6	Under 1 : 8.2 1– 4 : 2.4 5–19 : 4.0	
20–49	45.1		21.2		
50–64	13.6	19.9	22.6		64.2
65 and over	6.3		41.6		

* Interpreted from figures of Dublin and Lotka (2).

Since the incidence of positive reactors is increasing with the age, it is clear from this table that this incidence must be considerably higher among the dead than among the living of the same calendar year. Estimating the incidence of reactors among the dead above fifty years of age as 90 per cent, that among the dead between twenty and forty-nine as 60 per cent, that between birth and twenty as 10 per cent, which are cautious estimates, we get for the whole group of dead $64.2 \times 0.9 + 21.2 \times 0.6 + 14.6 \times 0.10 = 57.8 + 12.9 + 1.5 = 72$ per cent reactors. Considering that a part of the reactors later become negative and that, therefore, the attack-incidence of tuberculosis is higher than the incidence of reactors, and also that the dead of the life table population are some-

what older than the dead of the actual population because older age groups are larger in the life table population than in a growing actual population, we may safely accept 70 per cent as the *minimal* possible number for the attack-incidence of tuberculous infection among the dead of the life table population of the year 1937 in the United States.

As to the respective *maximal* number, this is hardly conceivable to be over 85 per cent, since 8.2 per cent of the dead of 1937 were under one year of age, and since it is very improbable that the attack-incidence of tuberculosis had reached fully 100 per cent among all the dead over twenty years of age.

Accepting 70 per cent for the minimal and 85 per cent for the maximal possible attack-incidence of tuberculous infections among the dead of the life table population of the year 1937, we get the following figures for possible minimal and maximal expected fatalities of tuberculous infection of the year 1937 in the United States:

White females	3.0%– 3.6%
White males	4.1%– 5.0%
Colored females	8.2%–10.0%
Colored males	9.7%–11.7%

It may be stated furthermore that the same estimates we have accepted for possible maximal and minimal attack-incidences of tuberculous infections among the dead of the life table population of 1937 can safely be accepted also for those of the life table population of the year 1920. The acceptance of the same minimal number does not need any explanation. The maximal possible number is determined by the percentage of deaths below one year of age, which was 15 per cent in 1920; 85 per cent can therefore safely be accepted as the maximal possible attack-incidence of tuberculous infection for the life table population of the year 1920.

The significance of this congruency as to the computation of the change in the fatality of tuberculous infections during the past decades is clear. Fatality, in our equation, is the ratio of the chance of the newborn of eventually dying from tuberculosis to the attack-incidence of tuberculous infection among the dead of the life table population. Since the maximal possible shift in the attack incidence of tuberculous infection among the dead of the life table population from 1920 to 1937 is confined to the values between 70 and 85 per cent, it can be almost neglected as compared with the definite shift during this period in the chances of the newborn of eventually dying from tuberculosis. The decline of the fatality of

tuberculous infection can be computed therefore to have been practically of the same range of magnitude as that of the chance of the newborn of eventually dying from tuberculosis, as shown in the figures above. This means that, during the last twenty years, the fatality of tuberculous infections among the white population of the United States has dropped to approximately one-half of its original value, nearly as much as the annual mortality rate of tuberculosis, which was 11.4 in 1920 and 4.7 in 1939. The slight discrepancy between the drop of the fatality and the drop of the annual mortality is mainly due to the increase of the average span of life during this period, giving now more time to the annual mortality to work than previously.

It would be, however, a mistake to believe that the diminution of the attack rate of tuberculous infections[6] had no part in the recent diminution of both the annual mortality rate and the fatality of tuberculous infections. The attack-incidence of tuberculous infections is an exponential function of the age, and the effect of a low attack rate, as compared with that of a higher one, is therefore much more pronounced in early than in old age. Though the number of those who finally escape infection has not much decreased, the age in which infection occurs has been considerably postponed. As a result, the number of those infected in early childhood, which is a specially dangerous age, has much diminished, and so has quite generally the time available for the infection to develop its full fatality. Both circumstances have favorably affected the fatality of the infected.

Our final question is: what is the chance of the freshly infected of the year n of eventually developing an open pulmonary tuberculosis. The answer is simple.

Number of the dead from open pulmonary tuberculosis developed from the infections acquired in the year n = number of the infections acquired in the year n $\times$ chance of the freshly infected of the year n to develop open pulmonary tuberculosis $\times$ fatality of open pulmonary tuberculosis. From which: Chance of the freshly infected of the year n to develop open pulmonary tuberculosis =

$$\frac{\text{Number of the dead from open pulmonary tuberculosis developed from the infections acquired in the year n}}{\text{Number of the infections acquired in the year n} \times \text{fatality of open pulmonary tuberculosis}}$$

[6] Attack rate of tuberculous infection in a community is the ratio between the annual number of new persons infected and the midyear population, expressed in hundreds (Hart (5)).

and since

$$\frac{\text{Number of the dead from open pulmonary tuberculosis developed from infections acquired in the year n}}{\text{Number of the infections acquired in the year n}}$$

is the definition of the chance of the freshly infected of the year n of eventually dying from open pulmonary tuberculosis, we get finally:

Chance of the freshly infected of the year n to develop open tuberculosis =

$$\frac{\text{Chance of the freshly infected of the year n of eventually dying from open pulmonary tuberculosis}}{\text{Fatality of open pulmonary tuberculosis}}$$

Figures for the numerator of our fraction should be correctly calculated in the same way as the chances of dying from all forms of tuberculosis. This would be a somewhat lengthy way, since we have no ready figures for chances of newborns of eventually dying from open pulmonary tuberculosis. But we can get practically the same results by multiplying the figures of the corresponding chances of dying from all forms of tuberculosis[7] with the fraction:

$$\frac{\text{Deaths from pulmonary tuberculosis}}{\text{Deaths from all forms of tuberculosis}}$$

This fraction was in 1937, both for whites and colored, males and females, very near to 0.9 (7).

There is no agreement about the fatality of those pulmonary conditions in which Koch bacilli can be sometimes detected by new, and laborious methods. But there is fairly good agreement about the fatality of the classical picture of open pulmonary tuberculosis, characterized by the constant and abundant presence of Koch bacilli. Whitney (8) has gathered lately the most important observations on this question. On the ground of her tabulation we will accept 70 per cent as a round figure for the fatality of open pulmonary tuberculosis, in the old sense of this expression.

[7] Chance of the freshly infected of the year n of eventually dying from tuberculosis = fatality of tuberculous infections of the year n.

Our computations gave the following figures:

Chance of the freshly infected of the year 1937 of eventually developing open pulmonary tuberculosis (minimal and maximal possible values, in percentages)

White females	$\frac{3.0 \times 0.9}{0.7} - \frac{3.6 \times 0.9}{0.7}$	= 3.8– 4.6
White males	$\frac{4.1 \times 0.9}{0.7} - \frac{5.0 \times 0.9}{0.7}$	= 5.3–·6.5
Colored females	$\frac{8.2 \times 0.9}{0.7} - \frac{10.0 \times 0.9}{0.7}$	= 10.6–13.0
Colored males	$\frac{9.7 \times 0.9}{0.7} - \frac{11.7 \times 0.9}{0.7}$	= 12.6–15.2

SUMMARY

In order to evaluate the toll of tuberculosis in the infected part of the population, definitions and methods of estimation are given for the annual fatality rate of tuberculosis, the expected fatality of tuberculous infections acquired in any given year and the chance of the freshly infected of that year to develop open tuberculosis.

Figures for these values are computed. These show that the toll of tuberculosis among the infected part of the population of the United States has greatly diminished during the twentieth century. This drop is the main cause of the corresponding diminution of the annual mortality rate of tuberculosis in this country.

Our results do not agree with those of Bogen (9).

SUMARIO

A fin de justipreciar el tributo cobrado por la tuberculosis en la porción infectada de la población, ofrécense aquí definiciones y métodos para calcular el coeficiente letal anual de la tuberculosis, la letalidad esperada en las infecciones tuberculosas adquiridas en cualquier año dado, y las probabilidades de que manifiesten tuberculosis abierta los recién infectados en dicho año.

Una comparación de las cifras demuestra la considerable disminución observada durante el siglo XX en los estragos ocasionados por la tuberculosis entre la porción infectada de la población de los Estados Unidos. Esa baja constituye la principal causa de la correspondiente disminución de la mortalidad anual ocasionada por la tuberculosis en Estados Unidos.

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TUBERCULOSIS SURVEY[1]

Observations in Schools of Rhode Island

WILLIAM P. SHIELDS

During the school year 1938–1939, an attempt was made to estimate the incidence of tuberculous infection and disease in the students of the school system of the State of Rhode Island. Following the trend of such investigations, this study was focused upon the high school groups, although a smaller number of other age groups was included for sake of comparison. The Mantoux technique was used to detect reactors, using the purified protein derivative of tuberculin in both first and second test strengths. Positive reactors had their chests X-rayed with a portable machine.

The plan of the work was similar to many others that have been used in this type of work; namely, a preliminary period of instruction including a sound film on tuberculosis, and an explanatory lecture describing the tuberculin test. Cards were sent home to parents to obtain the necessary consent for the test. Students showing X-ray evidence of disease were notified to contact their family physician, who simultaneously received a detailed report of the findings.

RESULTS

Including elementary, high school and college groups, 4,320 students were tested (table 1).

The question that now presents itself is in what manner do these figures compare with those from other areas with similar methods of procedure and concerned with similar groups.

It can be readily seen by examining table 2 that Rhode Island has a higher incidence of tuberculous infection than does the United States as a whole.

In table 3 is presented the tuberculin response for the various communities, together with a five-year average of mortality per 100,000 population in these communities. In the localities studied, we were

[1] From the Division of Child Hygiene, Rhode Island Department of Health, Providence, Rhode Island.

not able to find any consistent relation between the percentage of tuberculin reactors and the death rate from tuberculosis.

This experience casts some doubt in our own minds concerning the oft-quoted dictum of Myers, "that the tuberculosis problem in a community is measured by the relative frequency of the tuberculin reactors." Plunkett (1) has stressed recently the effect of other factors, such as race, society group, environment and economic status, on the mortality rate of tuberculosis. These factors may well be applied to our own experience and explain the lack of correlation.

TABLE 1

Results of Mantoux test with first and second strengths PPD

NUMBER TESTED	NEGATIVE	POSITIVE REACTIONS		TOTAL POSITIVE REACTIONS TO TUBERCULIN
		1st Test .000,02 mg. PPD	2nd Test .005 mg. PPD	
4,320	2,267 52.4%	1,350 31.2%	703 16.2%	2,053 47.5%

TABLE 2

Comparison of tuberculin testing with PPD in Rhode Island and United States (3)

AGE	NUMBER TESTED		PER CENT POSITIVE		PER CENT POSITIVE ADJUSTED FOR AGE	
	R. I.	U. S.	R. I.	U. S.	R. I.	U. S.
All ages	4,320	56,688	47.5	36.4	57.4	47.0
Under 5	14	1,450	21.4	24.6		
5–9	264	9,367	22.3	23.3		
10–14	909	17,598	45.2	33.4		
15–19	2,900	18,443	50.0	36.3		
20 and over	161	8,692	68.9	58.3		

Tuberculin reactors according to age and school groups: Chart 1 outlines the reaction in various age groups, as contrasted with similar groups in the United States (3). In the age groups particularly concerned in this study, namely, five to ten and ten to fifteen years respectively, this State shows between 15 and 20 per cent higher incidence of tuberculin reactors than similar age groups in the United States as a whole (3).

As will be noted in table 4, there are three groups—Elementary, High School and College.

In tables 5, 6, 7 and 8 is presented the tuberculin response in the various school groups, together with a comparison of such groups with that of other localities.

TABLE 3

Percentage of tuberculin reactors in students as compared with the mortality from tuberculosis in the same localities in the state of Rhode Island—1938–1939

SCHOOL	NUMBER IN SCHOOL	NUMBER TESTED	PER CENT TAKING TEST	NUMBER POSITIVE	PER CENT POSITIVE	DEATH RATE PER 100,000 POPULATION FROM TUBERCULOSIS—5-YEAR AVERAGE
Newport—DeLaSalle High	228	102	44	39	38	57.6
Barrington	222	47	21	24	51	27.1
Bristol—Colt High	309	229	74	119	49	74.4
Bristol—Guiteras Junior High	625	86	13	31	36	74.4
Burrillville	324	90	27	61	68	40.8
Central Falls High	616	247	40	141	57	48.6
Central Falls—Holy Trinity Private	561	351	62	142	40	48.6
Coventry	401	78	20	45	56	36.7
Cranston	1,664	249	14	121	48	22.4
Cumberland	546	142	26	79	55	62.6
East Greenwich	170	27	16	12	55	33.2
East Providence	1,097	614	56	334	54	48.8
East Providence—St. Mary's High	46	21	45	11	52	48.8
Newport—Roger's High	1,635	585	35	194	33	57.6
Newport—St. Joseph's High	135	38	28	11	32	57.6
North Kingston	162	42	25	20	47	32.5
R. I. College of Education	650	186	25	123	66	
Barnard School (Primary)	500	226	45	77	34	
South Kingston	388	145	38	58	40	32.2
Warren	321	176	54	94	53	61.5
Westerly	579	101	17	43	42	66.1
West Warwick	522	163	31	107	65	48.1
Woonsocket High	955	183	19	101	55	50.7
Woonsocket—Mt. St. Charles High	525	48	9	32	66	
Richmond (Primary)	296	144	48	34	23	61.8
Total—State of Rhode Island	13,427	4,320	32.1	2,053	47.5	46.4

X-ray findings: Three thousand, nine hundred and sixty-nine were examined, 1,850 of whom were X-rayed. Three students were found to have adult type tuberculosis. The incidence, then, of adult type tuberculosis among the 1,850 X-rayed was 0.16 per cent, and in terms

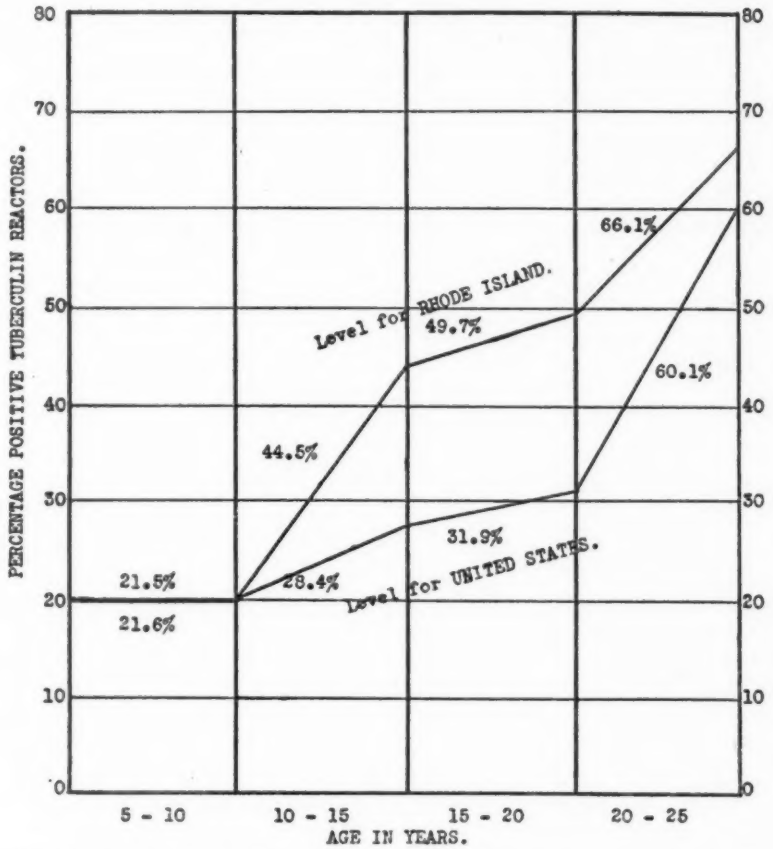

CHART 1. Tuberculin reactors in school children of Rhode Island by percentage in age groups, 1938–1939

TABLE 4

Reactors in various school groups to tuberculin

SCHOOL GROUP	NUMBER TESTED	PER CENT OF GROUP	NUMBER POSITIVE	PER CENT POSITIVE
High school	3,414	81.0	1,690	49.5
Elementary school	720	16.0	253	35.0
College	168	4.0	106	63.0
Teachers	18		17	94.4
Total	4,320			47.8

of the total number skin tested, it was 0.07 per cent. In other words, in examining 10,000 students, the great majority being high school students, one would expect to find 7 cases of adult type tuberculosis. Two of these cases in the female group, have moderately advanced disease, one is bilateral apical, age seventeen, and the other is unilateral with

TABLE 5

Tuberculosis survey in high schools of Rhode Island 1938–1939—results of Mantoux test with first and second strengths PPD

NUMBER TESTED	NUMBER NEGATIVE	POSITIVE 1ST TEST	POSITIVE 2ND TEST	TOTAL REACTIONS TO TUBERCULIN	PER CENT POSITIVE
3,414	1,724 50.4%	1,120 32.6%	570 16.6%	1,690	49.5

TABLE 6

The reaction of Rhode Island high school students to tuberculin compared to other localities

STATE	YEAR	TUBERCULIN USED	AGE	NUMBER TESTED	PER CENT POSITIVE
Rhode Island	1938–1939	PPD	13–20	3,414	49.5
Illinois (Chicago) (4)	1938	PPD	13–20	7,574	57.0
Pennsylvania (Philadelphia) (5).	1937	PPD	13–20	1,248	64.0
Massachusetts (6)	1938–1939	.01 mg. OT	13–20	81,141	22.2
Vermont (7)	1939	.01 mg. OT	10–19	5,065	26.0
Connecticut (New Haven) (8)...	1939	PPD	13–20	3,200	38.0

TABLE 7

Tuberculin reactors in elementary schools of Rhode Island

SCHOOL	NUMBER TESTED	PER CENT POSITIVE
Barnard	226	34.0
Richmond	144	23.5
Holy Trinity	351	40.4
Total	721	35

cavitation, age fifteen. The third case was in a young man, age seventeen, who had subclavicular strand-like infiltration, classed as minimal tuberculosis. This percentage is low compared to other studies (table 9).

In all these groups, except the Massachusetts group, PPD was used in both mild and strong dilutions In the Massachusetts group, .01 mg. OT was used. The type tuberculin used in the New York study is not revealed in that report.

TABLE 8

The tuberculin reaction of college students of Rhode Island compared to that of college students of other states

COLLEGE	NUMBER TESTED			AVERAGE AGE		PER CENT POSITIVE		TOTAL PER CENT POSITIVE
	Total	Male	Female	Male	Female	Male	Female	
R. I. C. E.	167	41	126	18.0	17.5	63.4	62.7	62.8
Yale	1,501	1,311	190	20.0	23.9	46.4	57.9	47.9
Bryn Mawr	416				18.5		46.5	46.5
Iowa State Teachers College	1,450	1,120	330	21.4	21.4	30.8	19.1	20.6
University of California, Berkeley	2,300	1,259	1,041	17.3	17.4	33.6	29.0	31.5
New Mexico State Teachers College	155	69	86	24.9	22.5	81.1	79.0	80.0
University of California, Los Angeles	213	213		20.2		57.7		57.7

TABLE 9

Comparison of X-ray diagnosis of adult type tuberculosis in high school groups

LOCALITY	NUMBER X-RAYED	NUMBER OF CASES OF ADULT TUBERCULOSIS
Rhode Island	1,850	3 (0.16%)
Massachusetts (6)	18,038	66 (0.36%)
Chicago (4)	3,883	22 (0.56%)
New Haven, Conn. (8)	1,509	11 (0.72%)
Philadelphia (5)	825	29 (3.5%)
Florida (10)	3,950	24 (0.61%)
New York City (11)	6,325	24 (0.38%)

TABLE 10

X-ray evidence of calcification in tuberculin reactors

SOURCE	NUMBER OF TUBERCULIN REACTORS X-RAYED	PER CENT SHOWING EVIDENCE OF CALCIFICATION
Present report	1,850	43.1
Green *et al.*	198	42.9
Gass	1,291	32.8
Myers	1,771	29.7
McKneeley	700	20.6

TABLE 11

Roentgenological summary

NUMBER X-RAYED	CASES OF ADULT TYPE TUBERCULOSIS	CASES OF HEALED CHILDHOOD TYPE TUBERCULOSIS	DOUBTFUL ADULT TYPE TUBERCULOSIS
1,850	3 0.16%	799 43.1%	49 2.6%

Healed primary lesions: X-ray evidence of a healed childhood lesion was found in 799 instances (43.1 per cent). A healed primary lesion was diagnosed when calcified foci were noted in the lung fields, either at the hilum, at the periphery or multiple foci scattered throughout the lung parenchyma. This incidence compares closely with other reports (12) as noted in table 10.

Table 11 summarizes the roentgenological data.

SUMMARY

1. The results are presented of a survey, in the School System of Rhode Island, to determine the prevalence of tuberculous infection and disease.

2. There is a high incidence of tuberculin reactors in the groups studied, but a low incidence of tuberculous disease. In Rhode Island we were not able to correlate the incidence of tuberculin reactors with the incidence of disease.

3. There was a fairly uniform rate of tuberculin reactors in groups representing different social and economic levels.

4. A high incidence of tuberculin reactors was found among school teachers. Since the number was small, we mention it only as it might merit further study.

5. Although for practical purposes of case-finding school children are not a good group for study, no one can deny the educational value and future benefits that might accrue to this age group in such a survey.

SUMARIO

1. Aparece aquí el resultado de un censo realizado en el Servicio Escolar del Estado de Rhode Island, para determinar la presencia de infección y enfermedad tuberculosa.

2. Se observó una frecuencia elevada de reactores a la tuberculina en los grupos estudiados, pero un coeficiente bajo de enfermedad tuberculosa, sin que se pudiera correlacionar un dato con el otro.

3. Fué bastante uniforme el coeficiente de reactores a la tuberculina en grupos que representaban diversos niveles sociales y económicos.

4. Hubo un coeficiente elevado de reactores a la tuberculina entre las maestras de escuela, pero como el número es pequeño, sólo se menciona el punto como acreedor a un estudio más detenido.

5. Aunque para fines prácticos del descubrimiento de casos, los es-

colares no constituyen un buen grupo para estudio, nadie puede negar el valor educativo de los estudios de esta naturaleza, y los beneficios que pueden acarrear en el futuro.

I am indebted to Dr. Edward A. McLaughlin, Director of Health in the State of Rhode Island, Dr. Ubaldo E. Zambarano, Superintendent, Rhode Island State Sanatorium, and Dr. James F. Boyd, Consultant Roentgenologist, State Department of Health, for their support and coöperation in making this study possible.

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VOLUNTARY DISCHARGES FROM A TUBERCULOSIS SANATORIUM[1]

E. K. JOHNSON

A major problem in the supervision of patients with tuberculosis is the prevention of contact with the nontuberculous population. Although there are many recommendations as to the best methods, it still seems that the tuberculosis sanatorium offers the logical solution. Here the patient is prevented from infecting the general population and therapy can be instituted. Furthermore, the organization serves as a unit for investigating those who were in contact with the patient and finding the minimal cases before they become advanced. A certain percentage of patients, because of various reasons, will not consent to be hospitalized while others refuse to remain until their disease is arrested.

This paper intends to reveal some of the reasons tuberculous patients leave an institution against advice. This question was discussed by Plunkett (1) in his article on *Tuberculosis Control* in which he presents the problems concerning these patients. He states that if the reasons are known then perhaps the remedies can be found. The importance of determining the cause of tuberculous patients leaving sanatoria against advice is apparent when we consider the mode of dissemination of the disease. If all contact between the tuberculous and nontuberculous population could be prevented, then human tuberculosis would be almost extinct by the next generation. As this is most improbable, our next possibility would be to control the active cases.

The control of tuberculous patients has been discussed and reviewed by many authors. Each believes the greatest benefits to the patients could be had in the average tuberculosis sanatorium. Very few reported the percentage of patients who left against advice and little or no information could be gleaned as to their reasons of departure. Because of the magnitude of this phase of tuberculosis control, a comprehensive survey was made of patients in a modern tuberculosis sanatorium. This institution, located in Central Ohio, admits patients in all stages of pulmonary tuberculosis, the great majority being charity cases.

[1] From the Licking County Tuberculosis Sanatorium, Newark, Ohio.

During a five-year period, 395 patients were discharged from this sanatorium. Of this number, 75 died in the sanatorium, 65 were released against advice and 255 were dismissed as arrested or transferred to other institutions. The 65 patients who left against advice were termed voluntary discharges and represent 16 per cent of the total group. If the 75 patients who died were deducted the voluntary discharge group is 22 per cent of those alive at their dismissal.

This seems to be in agreement with other data that can be found. At a tuberculosis sanatorium in Iowa about 34 per cent were given voluntary releases (2), and in a municipal hospital caring for advanced cases, the voluntary discharges were 40 per cent in the white and 65 per cent in the

TABLE 1

Comparison of the voluntary with the total discharge group

ITEMS OF COMPARISON	ALL PATIENTS DISCHARGED	VOLUNTARY DISCHARGES
Number of patients	395	65
Male	49%	34%
Female	51%	66%
Age in years	29.8	31.9
Number of admissions	1.3	1.5
Collapse therapy	36%	30%
Days in institution	133.2	152.0
Condition at discharge		
Unimproved	20%	35%
Improved	37%	50%
Quiescent	22%	15%
Apparently arrested	21%	0%

colored people (3). In Philadelphia, about 7 per cent of the patients with pulmonary tuberculosis in the general hospitals were given voluntary discharges (4).

The statistics of both groups are listed in table 1. This gives a summary of the groups leaving against advice and the total group being discharged during this five-year period.

In summarizing the statistics of both groups we see that they are similar as to age, number of admissions, hospital days and type of therapy used. They differ in sex ratio and response to treatment to a noticeable extent. As will be shown, the voluntary discharge group had marked personality changes, especially in regard to their emotions. This is in agreement with Eyre (5) who says patients having pulmonary tuberculosis with excessive emotions seldom secure effective cures. She states

that an active mind with a weak body promotes energy waste which defeats rest therapy.

In considering the reasons for patients leaving the sanatorium against advice, many angles were investigated to find what appeared to be the true answers. All patients did not state their reasons for voluntarily leaving the sanatorium as some left without permission. However, their behavior and emotions were often the best guide to their mental actions. The other patients who left with permission, but against advice, usually made some comment to justify their departure. The charts were checked for obvious reasons and most of the facts are derived from this source. In addition, the medical staff, social workers, nurses and patients were interviewed and from this collection of data the most evident reasons were formulated. Although it is improbable that all reasons are accurate, the majority seem fundamentally sound which is essential to any statistical survey.

TABLE 2

The different groups receiving voluntary discharges

GROUPS	NUMBER OF PATIENTS	CHARACTERISTICS OF EACH GROUP
Optimistic	16	Sanguine attitude, optimistic, euphoric, exuberant confidence in remaining "cured".
Introverts	12	Asocial and aloof, nonparticipation in coöperative groups.
Discouraged	9	Despondent attitude of hopelessness, periods of false cheerfulness.
Personal	9	Normal emotions and behavior, left because of personal problems.
Infantile	8	Egocentricity, hysterical reaction, display of petty jealousy and envy.
Homesick	4	Constant emotional depression, weeping, disheartened.
Skeptical	4	No abnormal personalities, disbelieved diagnosis of tuberculosis.
Extroverts	3	Arrogant attitude, uncoöperative, incite other patients to insubordination.

There are eight reasons under which all voluntary discharged patients were classified, the number resulting from a grouping of the various excuses and reactions, rather than any set classification. Many cases had several different reasons and as they had to be grouped singly, the paramount one was used. We wish to stress the fact that no patient had only the characteristics of his group, but may vary from time to time through different groups. A patient might be decidedly homesick yet show in

addition symptoms of infantile behavior, which would make the classification difficult. Nevertheless, it became apparent that one group of symptoms was outstanding in each individual during his stay here. We felt these patients would react similarly in other institutions which would verify our classification.

In table 2 are the reasons with the characteristic of each group receiving voluntary discharges at this sanatorium.

The eight groups who received voluntary discharges can be divided into two divisions by which the classification can be simplified. One division covers the patients who react as normal individuals; it constitutes 20 per cent of all those leaving against advice. The groups in this division are "Personal" and "Skeptical." In the other division are the remaining groups who have abnormal emotions and behaviors. Each exhibited some personality change which distinguished him from the others. The six groups in this division were 80 per cent of all those leaving against advice and 16 per cent of all those discharged alive during this five-year period.

COMMENT

It is improbable that any group of patients in tuberculosis sanatoria will ever be found who are all emotionally stable. Usually there are a few who have sufficient quirks of personality and differences in behavior to set them apart from the rest. Some authors state the majority of tuberculous patients are emotional with egocentric personalities, while others contend the greater portions are cheerful, courageous and self-sacrificing (6, 7, 8, 9, 10, 11, 12, 13).

Regardless of the contentions, minor mental disorders play an important part in tuberculosis. Breuer (14) observed that about 30 per cent of his series of cases exhibited psychic disorders of which 17 per cent showed severe progressive pulmonary tuberculosis as compared to 3.3 per cent in the psychologically normal patients. Peterson (15) reveals that, of 52 cases observed by social workers, only 36 per cent had a constructive attitude towards recovery. Forster and Shepard (16) analyzed 100 cases at Cragmor Sanatorium in which they found 31 patients in various emotional states. Morse (17) stated that in 100 cases of advanced pulmonary tuberculosis a large percentage gave evidence of anxiety, fear and emotional instability.

Undoubtedly some of the patients who receive voluntary discharges from tuberculosis sanatoria have exhibited their peculiarities of behavior

and personality since childhood. Others have concealed their emotional reactions and they only reveal them during a critical period. For many patients the crisis is reached when a diagnosis of pulmonary tuberculosis is made and they are advised to secure treatment in a tuberculosis sanatorium. This does not mean that the great majority of patients become uncontrollable and go to pieces. Williams and Hill (18) reported that only 4 per cent gave up hope when confronted with a diagnosis of tuberculosis and 18 per cent showed various emotional disturbances.

Ahrens (19) lists many of the changes which the patient must face in rearranging his life from the active phase to the quiet life in a sanatorium. This difficulty in adjustment is found throughout the general population, there being groups of people who change their personality and behavior when confronted by a difficult problem.

Many reasons have been offered to explain the mental state of the tuberculous individual. Ishigami (20) believes excitable emotional people have a lowered opsonic index which makes them more susceptible to disease. In this way tuberculosis or any other infection may occur more readily in these individuals. A similar explanation was made by Brown (11) who believed excessive emotions caused waste of nervous energy by raising the metabolic rate. This again places the emotions as a predisposing factor to infection.

Ross and Stanbury (21) state that a small group of tuberculous patients have psychotic changes, while others have excessive emotions, the latter resulting from the toxaemia of tuberculosis. Thompson (22) says it differently in that the toxins of tuberculosis accentuate the patients' emotions which had previously been concealed. Whether emotional instability predisposes towards tuberculosis or tuberculosis towards unstable emotions is a debatable question. From my study of these cases it seems the personality changes are not caused by tuberculosis but are accentuated by confinement in an invigorating atmosphere.

The incidence of minor mental disorders varies in the general population, but one commonly thinks a rather high percentage of individuals have abnormal behaviors. Hincks (23) stated in 1938 that he believed about 20 per cent showed such disorders. In a neuropsychiatric examination of college students at Harvard University, Cobb (24) reported in 1922 that 16.4 per cent had neurotic histories indicating "nervous instability." At the University of Minnesota the freshmen students completed a neuropsychiatric questionnaire which Morrison and Diehl (25) reported in 1924 as showing 17.8 per cent of men and 11 per cent of women having neurotic tendencies. These reports indicate that about 15 to 20

per cent of our general population in the young adult age group have minor mental disorders. This percentage is comparable to the incidence of mental behavior problems in tuberculous patients as herein reported.

One of the chief aims of a tuberculosis sanatorium is to prevent further dissemination of the disease. This is accomplished by isolation or restricted migration during which time bed-rest and collapse therapy heal the lesions and convert the sputum. Some patients fail to arrive at that stage because they cannot adjust themselves to the institutional life, while others have delayed seeking medical aid until they are beyond reasonable hope. After varying lengths of time many of these patients will leave the institution to infect the general population.

The reasons most patients leave a sanatorium against advice are their abnormal personalities. If we could predict which patients are apt to leave, then we might direct our therapy to making their sputa negative. This would require radical collapse therapy and, no doubt, many would become invalids, but with negative sputum they would not spread tuberculosis. For those patients who may not benefit from these measures we might follow Bracken's (26) suggestion, made in 1918, of committing the incorrigible tuberculous patients to a sanatorium.

SUMMARY

A group of patients were studied to determine their reasons for leaving a county tuberculosis sanatorium against advice. They varied from adolescents to past middle age and all stages of adult pulmonary tuberculosis were represented.

About 22 per cent of all living patients released from the sanatorium received voluntary discharges. In this group, 80 per cent had some emotional or behavior problems which were related to their leaving the sanatorium. These problems ranged from restlessness to marked depression.

A brief review of the relationship of personality to tuberculosis was presented. Patients leaving a sanatorium with emotional and behavior problems require psychological as well as phthisiological therapy. A suggestion was made that patients receive aggressive, radical collapse therapy before they leave against advice to prevent the dissemination of tuberculosis.

SUMARIO

En el grupo de enfermos aquí estudiado tratóse de determinar las causas que los impulsaron a abandonar, contra el consejo profesional, un sanatorio para tuberculosos. En su composición el grupo variaba de

individuos todavía en su adolescencia a otros que habían pasado la edad media, estando representados todos los períodos de la tuberculosis pulmonar del adulto.

Aproximadamente 22 por ciento de todos los enfermos vivos dados de alta del sanatorio recibieron el alta voluntaria, y 80 por ciento de este grupo estaban afectados por problemas emotivos o del comportamiento, que variaban de inquietud a abatimiento pronunciado, y guardaban alguna relación con la salida del sanatorio.

Preséntase también aquí una breve reseña de la relación de la personalidad con la tuberculosis. Los enfermos que abandonan un sanatorio asediados por problemas afectivos y del comportamiento, necesitan terapéutica psicológica así como tisiológica. Propónese, además, que a fin de impedir la propagación de la tuberculosis, los enfermos que abandonan el sanatorio contra el consejo del médico sean objeto de una colapsoterapia radical.

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WEATHER AND RESISTANCE IN PULMONARY TUBERCULOSIS[1]

Part II

W. F. PETERSEN, J. S. HOWE AND M. E. MILLIKEN

TUBERCULOSIS SUBJECT 4—ADVANCED CASE WITH CLINICAL IMPROVEMENT

The next case of the series concerned a man who was admitted to the Research and Educational Hospital on March 6, 1936 and who became ill at approximately the same time that tuberculosis subject 3 became ill.

Clinical History

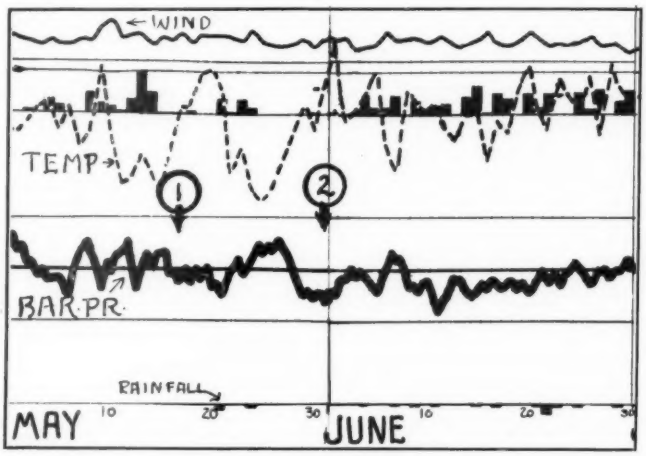
C. K., a fifty year old machinist, was in good health until May 17, 1934 **(1)** (text figure 17) when, two days before the Chicago Stockyards fire, he had a sudden sharp pain in his left chest and became short of breath. Pleurisy was diagnosed, his chest was strapped with adhesive, and he remained in bed a week before returning to work.

Two weeks after the onset of his pleurisy **(2)** he contracted a cold in his chest, with a productive cough and thick sputum containing bright blood for a period of two weeks. However, he sought no medical advice and continued light work. His cough and dyspnoea became progressively worse through the winter of 1934–1935. By the spring of 1935 he had become so dyspnoeic on slight exertion that he was unable to walk more than a few steps. He noticed marked fatigue and weakness, and a progressive loss of weight of at least 46 pounds (from 155 to 109 pounds) during the year.

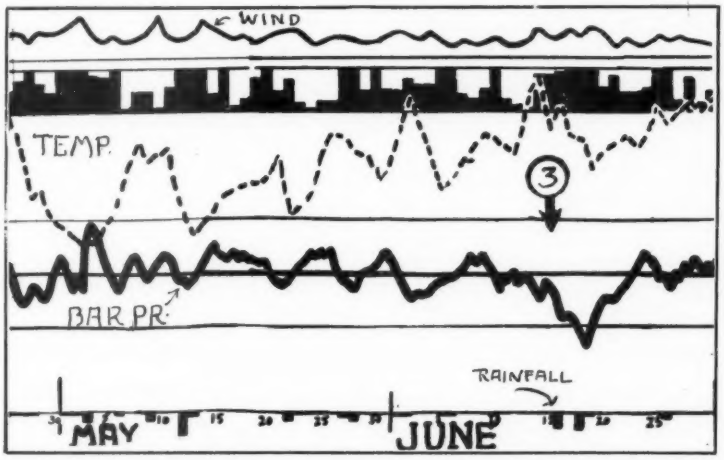
In May and June, 1935 he had noticed pain in his chest both right and left but worse on the left and more or less constant. On June 15, 1935 **(3)** (text figure 18) he became very weak and dyspnoeic and was taken to Cook County Hospital in an ambulance. Here he was on strict bed-rest for three months and was gradually allowed short walks. During his stay at Cook County Hospital he was bothered chiefly by a persistent cough and wheezing with dyspnoea on very slight exertion. He noted no cough before his attack of pleurisy in May, 1934. He was transferred to the Research and Educational Hospital on March 6, 1936.

[1] From the Department of Pathology, Bacteriology and Public Health, University of Illinois College of Medicine, Chicago, Illinois.

His past history revealed that he had mumps and measles as a child and gonorrhoea in 1903, with no complications. The family history was negative



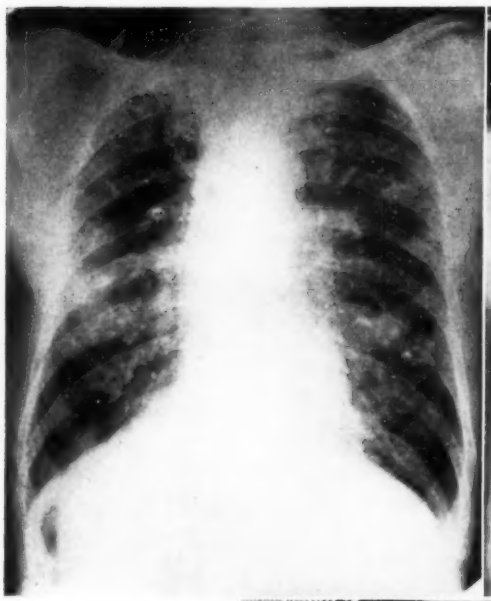
TEXT FIG. 17. Meteorogram to illustrate the onset (1) of productive cough (2) in tuberculosis subject 4.



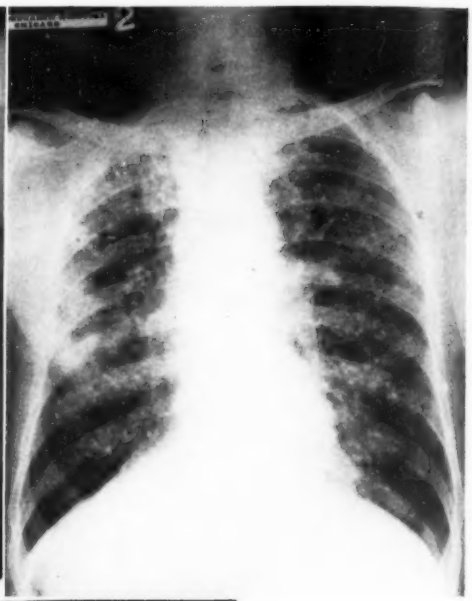
TEXT FIG. 18. Meteorogram to illustrate the meteorological situation at the time of admission to the Cook County Hospital. Note major turndown from high temperature on the 15th. (Tuberculosis subject 4.)

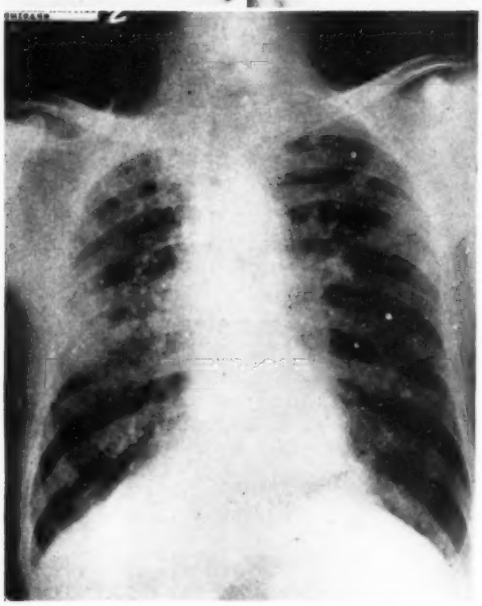
and there was no contact with tuberculosis. He drank from three to nine glasses of beer daily for years and whiskey at intervals; he was a moderate

ROENTGENOGRAM 8. March 4, 1936



ROENTGENOGRAM 9. June 17, 1936





ROENTGENOGRAM 10. March 11, 1937

smoker. He was employed for twenty-five years as a machinist, grinding castings with an emery wheel.

Physical examination revealed a well developed but poorly nourished man of about fifty years, not acutely ill but with a constant dry cough. Positive findings were: nasal septum deviated to the left; numerous teeth missing and many carious; cervical and inguinal lymph nodes palpable; moderately coarse râles over right chest to fifth rib posteriorly and over left chest posteriorly to fourth rib; increased breath sounds and whispered pectoriloquy in right subclavicular region; diminished tactile fremitus at right base posteriorly and in axilla.

The laboratory findings showed the Kahn test and urine to be negative. The haemoglobin was 13.0 g.; the red cell count 5,280,000; the white cell count 10,800.

Roentgenological examination made March 4, 1936 (roentgenogram 8) showed nodular infiltrations in both lungs extending outward from the hilum regions most markedly on the right side in the middle lung field. There was also increased density over the right apex and first interspace with irregular infiltrations in the latter. These findings were suggestive of pulmonary tuberculosis associated with silicosis.

Examination made June 17, 1936 (roentgenogram 9) showed probable increase of findings in right upper lobe suggestive of extension of tuberculous process.

Examination made March 11, 1937 (roentgenogram 10) showed almost identical findings to those of March 12, 1936.

The Weather at Periods of Activation

When we examine the meteorogram (text figure 17) we note that the onset on the 17th of May followed the same cold wave already observed in tuberculosis subject 3 **(1)**. Two weeks after the onset **(2)** he observed a productive cough. Apparently this was to be associated with the major tropical episode evident in the meteorogram. The following spring (text figure 18) there was an increase in symptomatology and on June 15 **(3)** he was finally taken to the County Hospital. It was to be noted that this unusual feeling of weakness was associated with sharp increase in environmental temperatures and marked precipitation, indicative of the severity of the environmental shift in atmospheric conditions.

Inasmuch as several patients were under observation during this time we can definitely state that violent biochemical and clinical alterations were induced by this situation (11).

The Biometeorogram

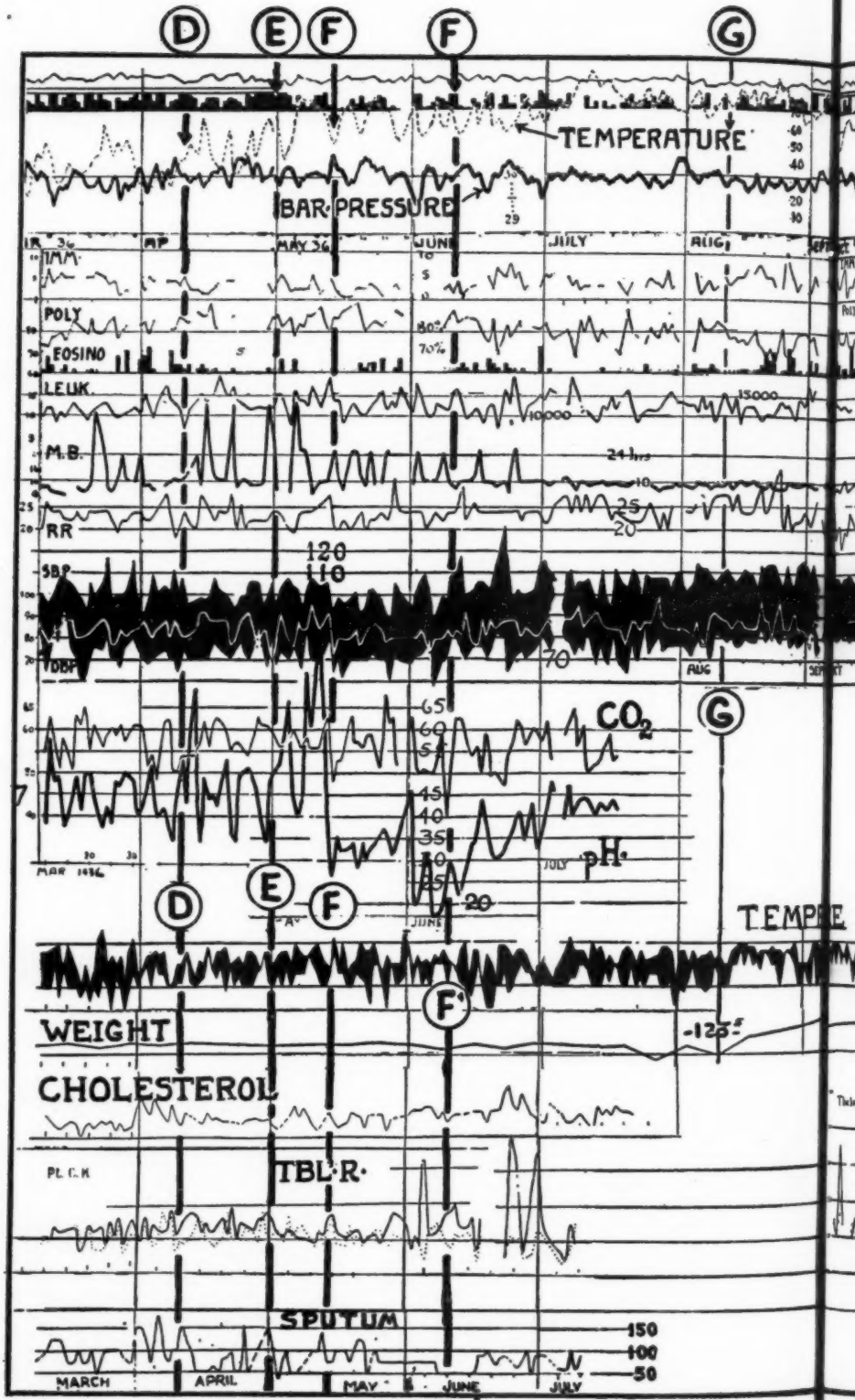
The biometeorogram (text figure 19) has the following superimposed curves:

(1) Meteorogram
(2) Immature forms
(3) Polymorphonuclear leucocytes
(4) Eosinophils
(5) Total cell count
} Blood cells
(6) Methylene blue disappearance time
(7) Respiratory rate
(8) Systolic blood pressure
(9) Pulse rate
(10) Diastolic blood pressure
(11) Medication (black bars)
(12) CO_2 content
(13) Blood pH
(14) Daily maximal and minimal temperatures
(15) Weight
(16) Cholesterol
(17) Quantitative tuberculin reaction
(18) Sputum volume
(19) Weltmann reaction

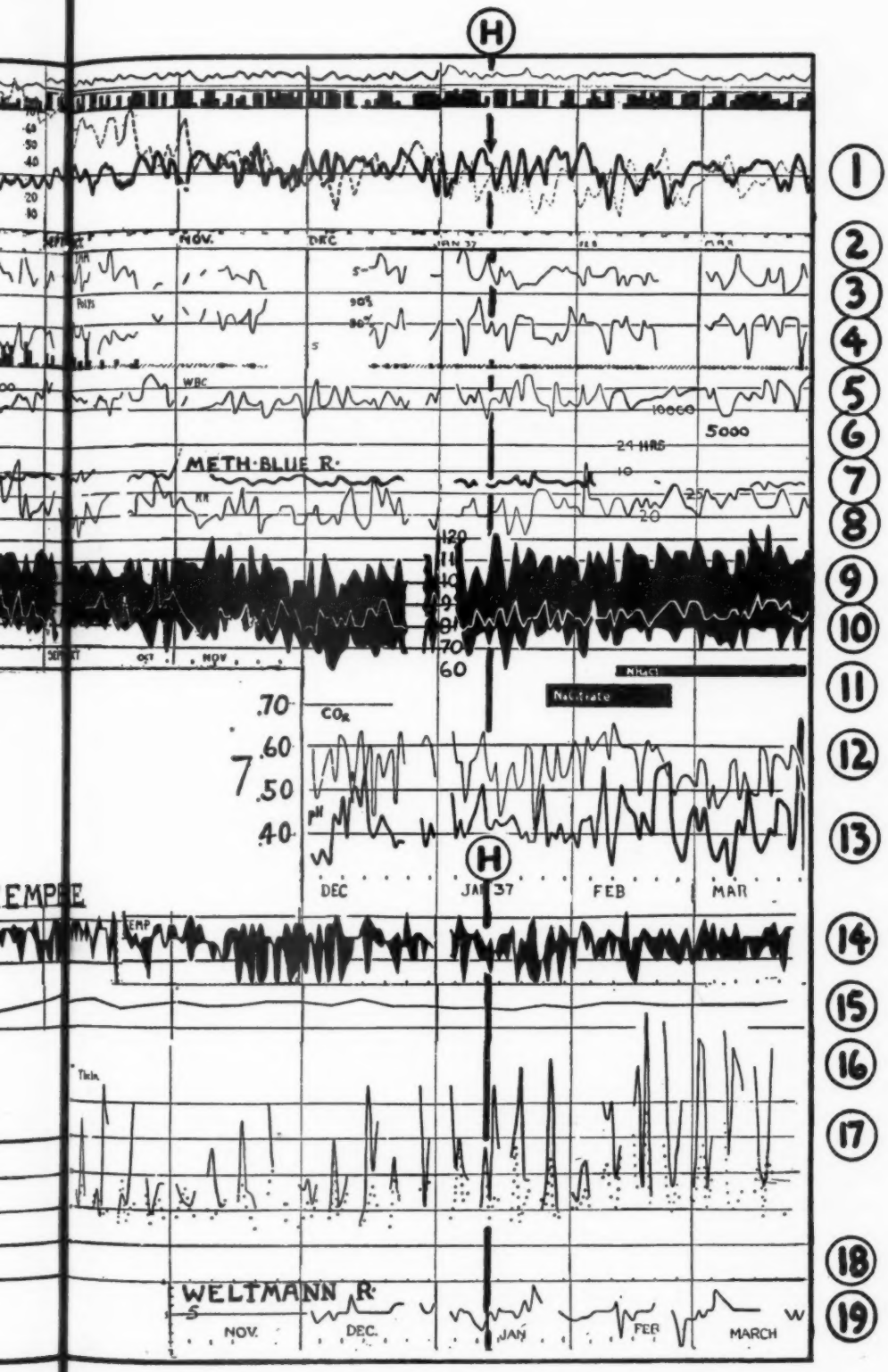
Clinical Notes

1936		
Mar.	9	Dyspnoea
	10	Cough worse
	11	Chest pain
	12	
	13	Chest pain; cough
	14	
	15	Cough; tired
	16	
	17	Severe dyspnoea; cough
	18	Dyspnoea; tired
	19	Dyspnoea
	23	Severe cough; dyspnoea
	24	Severe cough; dyspnoea
	25	
	26	
	27	Cough; abdominal pain
	28	Chest pain; abdominal pain
	29	Chest pain; dyspnoea
Apr.	1	"Cold"
	2	Dyspnoea
	5	Dyspnoea; cough
	6	
	7	Cough; dyspnoea
	8	Cough
	9	Cough; severe dyspnoea; chest pain
(D)	10	Dyspnoea; chest pain
	13	Tired
	14	Feels better
	15	Feels better
	16	Cough; dyspnoea; tired
	19	Chest pain; cough
	21	Precordial pain; cough
	22	Cough
	24	Headache
	27	Dyspnoea
	28	Cough
(E)	29	Cough; headache
May	4	Cough; slept poorly
	11	Cough
	12	Cough; dyspnoea

13 Tired
(F)14
15 Cough; dyspnoea
16 Cough; dyspnoea
17 Cough; dyspnoea
18 Cough; dyspnoea
19
20 Cough; dyspnoea
21
22 Tired
23
24 Cough; slept poorly
25 Cough
26 Tired
27 Cough
28 Feels better
29 Feels better
30 Feels better
31 Cough
June 1 Better
2 Better
3 Better
4 Better
5
6 Cough; slept poorly
7 Cough; slept poorly; tired
8
9 Cough
(F')10 Cough; dyspnoea
11 Cough; dyspnoea
12 Tired
13
14 Dyspnoea
15
16 Cough; dyspnoea
17 Cough; dyspnoea
18 Cough; dyspnoea
19
20 Cough; dyspnoea; slept poorly
21 Cough; dyspnoea; slept poorly
22 Cough; dyspnoea; slept poorly
23 Cough; dyspnoea; slept poorly
24 Cough; dyspnoea; slept poorly
25
26 Cough; slept poorly
27 Slept poorly
28 Much better
29 Much better
30 Much better
July 1 Much better
2 Much better
3 Much better
4 Much better
5 Cough
6
7 Cough
8 Cough; slept poorly
9 Feels better
10 Feels better
Oct. 20 Chest pain; cough; dyspnoea
21 Poor night; headache; nasal obstruction
22 Poor night
23
24 Cough; slept poorly
25 Dyspnoea; wheezing
26 Dyspnoea; wheezing; choking spells
27 Dyspnoea; wheezing; cough
28 Slept poorly; cough
29 Tired
Nov. 1 Cough; slept poorly
2 Tired
3
4
5 Cough; dyspnoea; wheezing
6 Tired
7
8 Severe cough; dyspnoea; wheezing
9 Tired
10
11 Dyspnoea; cough; wheezing
12 Dyspnoea; cough; wheezing
13
14
15 Cough; dyspnoea; wheezing
16 Cough; dyspnoea; wheezing
17
18 Marked dyspnoea; wheezing
19 Dyspnoea; wheezing
20
21
22 Dyspnoea; wheezing; cough
23 Dyspnoea; wheezing; cough
24 Chest pain; dyspnoea
25 Tired; headache
26
27 Chest pain; dyspnoea; wheezing
28 "Cold"; headache
30 Tired
Dec. 1 Wheezing; dyspnoea; tired
2 Wheezing; dyspnoea



TEXT FIG. 19. Biometeorogram of tube 4.



n of tube 4. (See text for detailed description.)

	3	Tired
	6	Cough; dyspnoea; wheezing
	11	Poor night; cough; dyspnoea
	12	Tired
	13	
	14	Cough; dyspnoea; tired
	15	Cough; restless night
	16	Drowsy
	17	
	18	Wheezing
	19	Drowsy
	20	Chest pain
	21	Chest pain; tired
	22	Chest pain
	23	
	24	Right chest pain
	30	Wheezing
1937		
Jan.	3	Restless
	4	Restless; cough; dyspnoea
	5	Tired; dyspnoea
	6	Tired; dyspnoea
	11	Drowsy
(H)	12	Headache; dyspnoea; orthopnoea
	13	Dyspnoea
	20	Choking spell
	21	Choking spell; dyspnoea
	22	Choking spell
	23	
	24	Choking; dyspnoea; orthopnoea
	25	Choking; dyspnoea
	26	Dyspnoea; began Na-citrate
	27	Tired
	28	Wheezing
	29	Dyspnoea
	30	Dyspnoea; orthopnoea; worst night
	31	Dyspnoea
Feb.	1	Dyspnoea
	2	Drowsy
	3	Restless; choking spells
	4	Dyspnoea; choking spells
	7	Headache; cough; choking
	8	
	9	Dyspnoea
	10	Began NH_4CL
	11	Drowsy
	12	Choking
	13	Headache
	17	Choking spell
	18	Choking spell
	19	Choking spell
	20	
	21	Dyspnoea
	22	Cough; dyspnoea; orthopnoea; palpitation
	23	Dyspnoea
	24	Dyspnoea; orthopnoea
	27	Cough; dyspnoea
Mar.	1	Choking spells
	2	Choking spells
	3	Dyspnoea
	4	Dyspnoea
	9	Cough; dyspnoea
	10	Cough; dyspnoea
	11	
	12	Bad night; dyspnoea; choking
	15	Dyspnoea; choking
	17	Drowsy; dyspnoea
	19	Choking
	20	Choking; drowsy
	21	Choking
	22	Cough; dyspnoea
	23	
	24	
	25	Intoxicated
	26	Released

As in the companion case we shall merely select a few clinical episodes for analysis during this long period of study. Here episodes have been lettered **(D)**, **(E)**, **(F)**, **(F′)**, **(G)** and **(H)** to correspond to the similar dates in the preceding case. **(F′)** has been added because in this patient this period represents evidence of maximal fatigue. **(G)** (at which date our preceding patient died) was here associated with an obvious upturn, while at **(H)** the effect of the typical midwinter polar episode can be followed.

General trends: The record is of interest because in this patient we can

(*1*) observe the effect of lessening of environmental turbulence and of increased environmental temperatures of the summer on the general improvement of the patient; (*2*) the fact that the meteorological situation which in our preceding patient had given the final *coup de grâce* **(G)** was here associated with the onset of improvement. In other words, that for the tuberculous individual the old adage that "one man's meat is another man's poison" can be definitely true.

Maximal spring acidity is revealed at **(F′)**, at the same time blood pressure levels were lowest (when we return to an examination of tuberculosis case 1 we find a history of clinical activation at this time).

After this period **(F′)** the following changes occurred:

(*a*) The methylene blue reaction time became more stable.
(*b*) Blood pressure increased.
(*c*) Blood pH increased.
(*d*) Cholesterol increased.
(*e*) Tuberculin reaction increased.

The effect of summer: A crest in blood pressure was reached in September; eosinophils increased during August, September and October, and this was also true of the immature forms; the respiratory rate decreased and there was a lowering of body temperature during October, November and December. Weight increased strikingly after episode **(G)**.

We turn now to a more detailed examination of the individual episodes:

Episode **(D)**: This date had been selected at a characteristic pressor crest in the preceding subject.

In this subject blood pressure had increased moderately the day previously. More striking is the maximal increase in blood pH which here follows an unusually low level. The methylene blue time was reduced, there was an increase in the respiratory and pulse rate, the temperature and sputum volume increased. The patient complained of severe dyspnoea and chest pain.

Episode **(E)**: This represented a period of unusually low blood pressure in our case 3. In this patient it was associated with a moderate decline in blood pressure and with a very low blood pH on the preceding day. The methylene blue time was decreased, there was an increase in pulse rate, temperature and cholesterol following the episode. The sputum volume increased and the patient complained of headache on the preceding day.

Episode **(F)**: In our preceding case 3 the period was one of maximum

change from high to low pH, from high to low blood pressure, a rapid decline in the tuberculin reaction, etc. Similar reactions are to be discerned in the blood pressure and pH curve in this patient. The patient felt very tired.

Episode **(F′)**: This period, as already mentioned, represented the biological low of the spring; diastolic lows were reached on June 6 and this was also true for the pH level. Morning temperatures reached a low on the 13th. The tuberculin reactions were reduced while the respiratory rate increased to a crest for the month at the same time. Then follows a major blood pressure crest.

Episode **(G)**: On this date our preceding patient died.

In patient 4 weight began to increase progressively from this date on. The morning temperatures were at a definitely higher level, the blood pressures maintained a higher level while the respiratory rate declined and eosinophils and lymphocytes increased.

It becomes evident that an environmental situation of minimal temperatures after the high temperatures of July 10 (which represented mortal strain for the preceding case) was in this case followed by a clear-cut swing toward improvement.

Episode **(H)**: This improvement, as already discussed, continued, the patient being finally discharged because of unruly behavior. What the ultimate clinical course was we do not know.

DISCUSSION

In this subject we can associate improvement (or its relative equivalent, quiescence) with environmental quiescence and observe that a meteorological situation which in the preceding case was associated with death here pushed the organism over to a phase of sustained improvement. In view of the basic mechanisms involved this paradoxical effect need cause no surprise. It will be discussed in detail later.

TUBERCULOSIS SUBJECT 5—TERMINAL MENINGITIS

Our next patient, a white male, was admitted to the Research and Educational Hospital on April 13, 1937 with the following history:

Clinical Record

L. L. was a twenty-two year old white male woodworker who was admitted to the Research and Educational Hospital on April 13, 1937 **(4)** (text figure 20) with complaints of chest pain, cough and sore throat of two weeks' duration.

He was perfectly well until February, 1937 when he first noticed nausea and vomiting on arising in the morning and occurring about three times weekly. In March, 1937 he consulted a physician who treated him with diet and pills, with some relief.

Two weeks before admission (March 13, 1937) **(1)** he noticed a pain in his left chest and axilla, dull in character and continuous. Three days later, about April 3 **(2)**, he began to cough up thick yellowish material. A week later, about April 10 **(3)**, he noticed a sore throat and abdominal tenderness which he attributed to the cough. In the two weeks before admission he lost 20 pounds in weight (text figure 20).

His past history revealed that he had had measles as a child, an operation on his right leg in 1922, and that his general health had always been good. He had smoked two packs of cigarettes daily, prior to the past two weeks. He used alcohol consistently, consuming two shots of whiskey daily and a pint on Saturdays, in addition to half a gallon of beer weekly. The family history was essentially negative.

Physical examination revealed a thin, pale man of twenty-two years, who seemed quite ill and coughed frequently. Head, eyes, nose, ears and oral cavity were negative except for slight injection of the pharynx. The heart borders were clear and regular and no murmurs were heard.

The lungs revealed bronchial breath sounds over the left upper chest with moderately coarse râles in the same area. The percussion note was resonant throughout. The abdomen showed no masses, rigidity or tenderness. The genitalia were those of a normal male. The extremities were normal.

The Wassermann and Kahn tests and the urine were negative. The blood picture showed: haemoglobin 9.0 g.; red cells, 4,330,000; white cells, 12,450; 87 per cent polymorphonuclears.

His course in the hospital was as follows:

April 21, 1937: Initial pneumothorax left chest.

April 23, 25, 29 and May 9: Pneumothorax refills.

May 17: 350 cc. fluid removed from left chest. (Guinea pig negative.)

June 1: 350 cc. fluid removed from left chest.

June 16, 23, 30: Pneumothorax refills.

July 3, 7, 11: Pneumothorax refills.

August 3: Left phrenicoexairesis.

October 21: Thoracoplasty advised by Dr. Van Hazel but refused by patient.

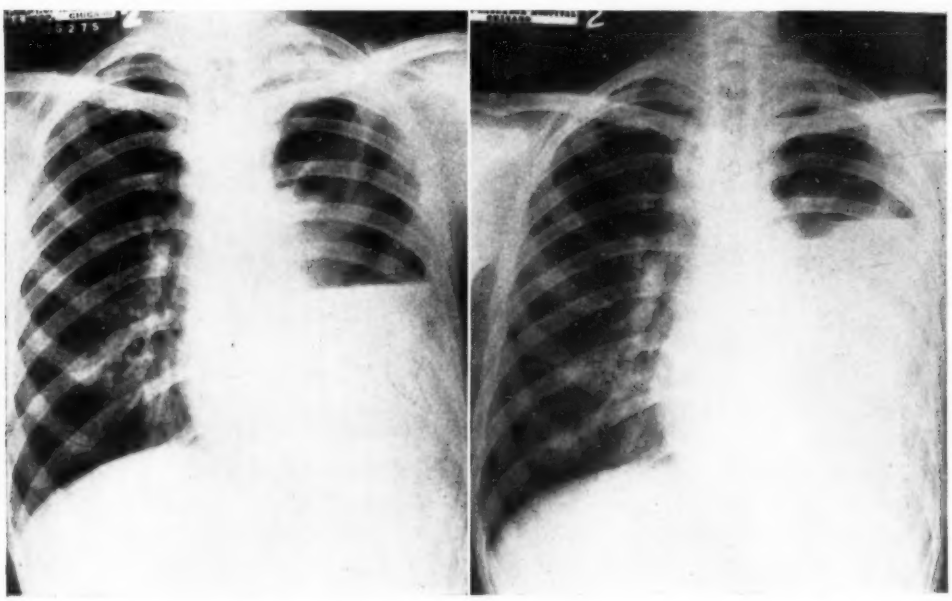
December 18: First evidences of tuberculous meningitis.

January 30, 1938: Patient was found lying on floor beside bed; he responded poorly; his neck was rigid and pupils were dilated, the right being larger than the left.

January 31: Expired.

Roentgenological examination made on April 14, 1937 showed irregular densities in the upper part of the left lung and the mediastinal structures displaced toward the left. The findings were consistent with pulmonary tuberculosis. Another roentgenogram made on April 26 showed a left hydropneumothorax with mediastinal shift to the right.

Examination made August 27, 1937 (roentgenogram 11) showed left lung collapsed with parts of upper lobe near the apex. Fluid was present in the left pleural cavity with fluid level at about the level of the sternal end of the fourth rib. On the right side there was increase of hilum shadows and linear

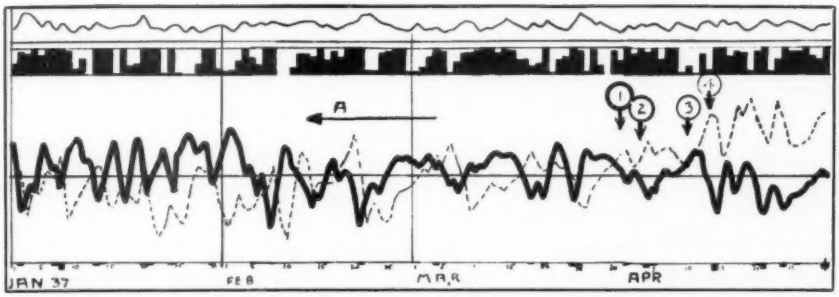


ROENTGENOGRAM 11. August 27, 1937 ROENTGENOGRAM 12. January 3, 1938

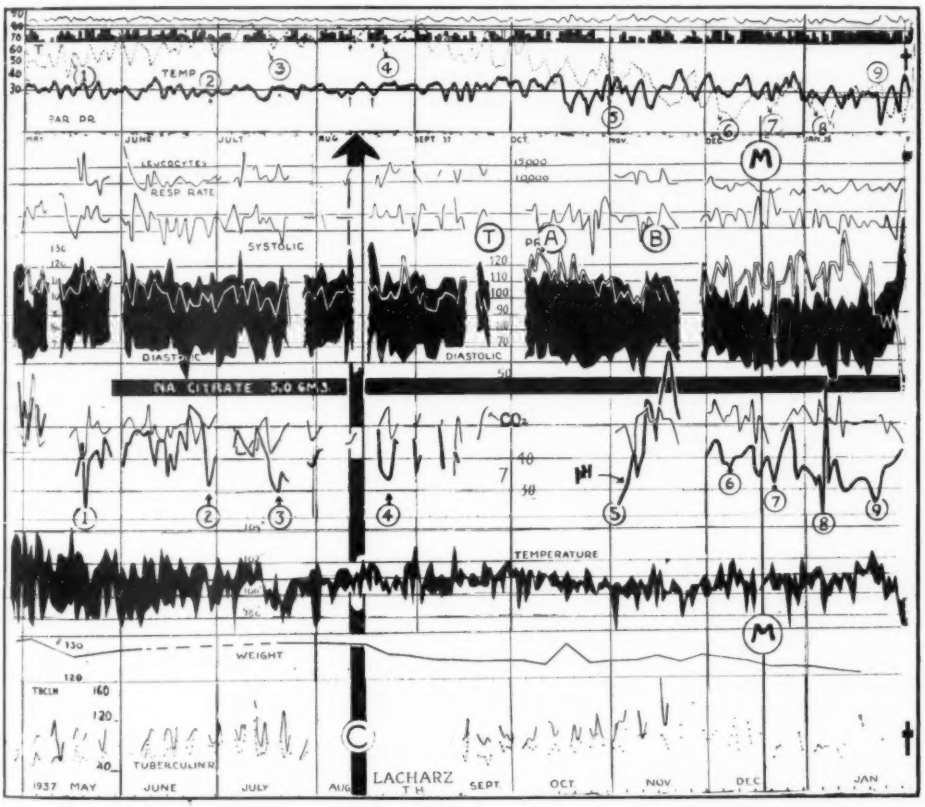
markings but no parenchymal infiltrations. Examination made January 3, 1938 (roentgenogram 12) showed the right lung practically the same as on the previous examination. On the left side the amount of fluid had increased so that the fluid level extended to the sternal end of the second rib.

The Weather at the Time of Activation

In this instance the onset of the acute symptomatology coincided with a period of severe cold that prevailed in Chicago during the latter part of January and the early part of February, 1937 when this patient first had nausea and vomiting. **(A)** (text figure 20) marks the beginning of illness; note severe cold.



TEXT FIG. 20. Meteorogram to illustrate the clinical events in tuberculosis subject 5.



TEXT FIG. 21. Biometeorogram of tuberculosis subject 5. (See text for detailed description.)

On or about March 31 **(1)** he developed a cough and chest pain. Examination of the meteorogram indicated that this followed a rather prolonged period of high barometric pressure and a crest of cold on the

26th of the month. With this marked precipitation was evident. On April 3 **(2)** the sputum became purulent (following the passage of another minor polar air mass) and on the 10th **(3)** he observed a sore throat. This was associated with a continued rise in barometric pressure and the crest of the cold wave. Three days later he was admitted to the hospital **(4)**.

The Biometeorogram

The graph (text figure 21) follows the general construction previously used.

A meteorogram has been superimposed, below this follow the curves of the daily leucocyte count, the respiratory rate, the systolic and diastolic blood pressure field (pulse rate indicated in the white curve in the black field).

The pH and CO_2 content of the blood is indicated, then follow the daily maximal and minimal temperature, the weight of the patient, the quantitative tuberculin reaction.

Clinical Notes

1937				25	
Apr.	27	Hoarse		26	
	28			27	Poor night
	29			28	Tired
	30			29	Head cold
May	1			30	
	2			31	
	3		June	1	
	4	Cough worse		2	Night sweat
	5			3	Night sweat; restless
	6			4	
	7			5	
	8			6	Restless night
	9			7	
	10			8	
	11			9	
	12			10	
	13			11	
	14			12	
	15	Pain left chest		13	Cough worse
	16			14	
	17			15	
	18			16	
	19	Cough worse		17	
(1)	20			18	
	21			19	
	22			20	
	23			21	
	24			22	Night sweat

23 Tired
24
25
26
27 Pain left chest; drowsy
(2)28
29
30
July 1 Tired
2
3
4
5 Poor night; cough worse
6
7
8 Poor night
9 Tired
10
11
12
13 Drowsy
14
15
16
17
18
19
(3)20
21
22
23 Cough worse; drowsy
24
25 Poor night; cough worse
26
27
28
29
30
31
Aug. 1 Emesis
(C)11–16
(4) 23
Sept. 12 Emesis
24 Tooth extracted; poor night—(T)
25 Tired
26
27
28 Severe cough; dyspnoea
29
30
Oct. 1 Poor night
2
3 Perspiring profusely
4 Poor night; cough worse
5
6
7
8 Cough severe; pain left chest
9
10 Cough worse; pain left chest and jaw
11 Tired
12
13 Sore throat; hoarse—(A)
14 Pain left chest
15 Pain left chest
16 Pain left chest; very hoarse; sore throat
17
18
19
20
21 Poor night
22 Tired
23 Poor night
24 Tired
25 Restless night
26 Tired
27 Cough worse; chest pain
28
29
30
31
Nov. 1 Poor night
(5)2 Tired
3
4 Poor night
5 Tired
6
7
8 Poor night; cough worse
9 Tired
10
11
12
13
14 Poor night; cough worse
15 Poor night
16 Cough worse; sore throat—(B)
17
18
19

20	Cough worse	25	
21		26	
22	Tired; pain left jaw	27	
23	Abdominal pain; nausea	28	
24		29	
25		30	Drowsy
26	Vomited	31	
27		1938	
28	Cough worse	Jan. 4	Cough; poor night
29	Cough worse	5	Tired; epigastric pain
30	Dyspnoea	(8)6	Poor night
Dec. 1	Pain left chest	7	Tired
2		8	
3		9	
4		10	
5	Nausea; emesis	11	Cough worse
6	Poor night; cough worse	12	
7	Tired; left chest pain; nausea; emesis	13	Poor night
		14	Tired
(6)8	Sore throat	15	Head cold; cough
9		16	Head cold
10	Restless night; hoarse	17	Headache
11	Tired; hoarse	18	Headache
12	Hoarse	19	Occipital headache
13	Sore throat; hoarse	20	
14	Poor night; cough worse; sputum increase	21	
		22	
15	Tired; emesis; diarrhoea	(9)23	
16		24	Poor night
17		25	Tired; emesis
(M)18		26	
19	Back and neck stiff	27	
20		28	
21	Restless; cough; emesis	29	Poor day; refuses food
(7)22		30	Drowsy; emesis
23	Restless night; tired	31	Comatose
24	Tired	Feb. 1	Expired

In this case we shall be interested solely in determining the time and cause of the ultimate breakdown of resistance to the infection.

For this purpose the heavy upright arrow has been drawn in text figure 21 from the period of August 11 and extending to August 16. The reader will keep this arrow in mind as a focal point **(C)**.

In addition, periods of low pH value in the serum have been indicated by circled numbers **(1)–(9)** in the lower part of the pH curve and corresponding numbers are indicated in the meteorogram above.

We have already stressed that the patient suffering from tuberculous infection succumbs to fatigue. In using this term we do not desire to

hide under an accommodating shelter of generalities, but we mean the definite organ status that we have discussed as the COD phase, when the peripheral venous blood becomes more acid, blood pressure is low, smooth muscle tends to be relaxed, the metabolic rate is increased (or we may have exhaustion), the cell membranes are more permeable, enzymes are diffusing out, capillary permeability is increased, etc.

In this instance we have noted such periods of lowered pH as landmarks that would correspond to such periods of fatigue; these have been numbered, as already stated, from **(1)–(9)**.

First of all it should be observed that the season of observation was favorable for the tuberculous patient. Environmental temperatures had been increasing from the time when the observations began.

When first observed the patient had a high temperature, with a wide amplitude of approximately 6°F. The blood pressure revealed a period of rather low diastolic levels, the pH was relatively high.

The first low pH **(1)** was recorded as of May 20. This followed a pressor crest on the 19th (that is, the causative anoxia). Fever and leucocytes were increased, the respiratory rate increased, the patient's cough was more severe, according to the record on the 19th.

Examination of the event revealed the fact that the episode followed a sharp fall in environmental temperature (to the 14th of the month) which in turn had been succeeded by another episode, with a polar front evident on the 17th when there was rain, etc. This second barometric episode was dual in character and typically this was associated with a dual blood pressure crest.

The next low pH value **(2)** occurred on June 28. This, too, followed a cold wave, which began on the 25th. The patient apparently withstood this episode without much reaction. However, the patient had pain in the left chest and he felt drowsy. A febrile crest was reached on July 1.

Medication—sodium citrate: Sodium citrate had been given since the latter part of May. The fact that the morning level of the temperature began to be raised shortly after this may be ascribed to the citrate, or may have been due solely to the change in environmental temperature. It is possible, too, that the resistance of the patient had been increased by this administration of an alkali.

Another low pH level was recorded on July 20 **(3)**. Again we witness that it occurred in the wake of the decline in environmental temperature and with a barometric crest. With this general period we observe wider

range in the tuberculin reaction. The patient complained that his cough was worse.

Up to this time the patient had been holding his own. The weight had been maintained, the general pressure levels of the blood had increased, the leucocyte count, pulse rate, respiratory rate had not increased.

On August 11, we witness a change for the worse; the blood pressure suddenly increased after it had been unusually low on the preceding day. This was evidence of a major autonomic disturbance (here observe the vertical arrow **(C)**).

A single episode of this kind might have been equilibrated but we note that there is a repetition of precisely the same situation on the 17th and 18th of the month, that is, before the patient had time to adjust to the preceding severe episode.

The reason for these major pressor crests was to be found in the meteorological situation of the time, namely, the passage of polar air masses. Note precipitation of 1 inch of rain on the 15th, and continued rain on the 17th, 18th and 19th, with falling temperatures. The possible pressor effect may have been accentuated because of the artificial increase in alkalinity, due to the large doses of citrate. This increase in alkalinity would increase the tone of the smooth musculature of the blood vessels, with a resulting unusual increase in the blood pressure levels. With this an unusual degree of anoxia might be expected to follow.

The critical decline of the patient began now. Weight declined, pH declined to a low level on the 23rd **(4)**. A febrile crest was in evidence on the 31st of the month. Of significance is the increase in the pulse rate to 126 per minute on the 28th of the month.

The resistance having been broken, every further change in the air mass was now followed by progression of the disease because with each change further energy was required.

Major acid peaks were witnessed at **(5)**, **(6)**, **(7)**, **(8)**, **(9)** (the first being followed by an amazing reversal to an alkalotic crest on the 19th[2]) each occurring as an aftermath of major polar episodes indicated at the corresponding numbers in the meteorogram.

On December 18 the patient developed evidence of meningitis **(M)** when his back and neck muscles were stiff. The symptoms of this complication developed progressively.

If we attempt to reconstruct the biological picture that was associated

[2] Observe the spectacular effect in the tuberculin reaction with this chemical reversal.

with the onset of the meningitis, we first observe that with December 10 environmental temperatures had reached a temporary low (6) and the blood pH had declined sharply from the great autumnal crest of November 19 (that is, a transient crest in resistance) to the period already described. Then we observe a spurt in the pH level on December 15 and with this there was a transient increase in the blood pressure followed by rapid shifts in the respiratory rate. Then blood pressures fell, the pulse rate increased, the pH declined, as did the leucocytes and body temperature. This latter reached its lowest point on December 15. Under such conditions we can assume that mass dissemination of bacteria may have occurred, with symptoms becoming evident within the course of the next two or three days.

Death followed forty-five days later, with a major barometric crest and with final effort of the vascular system to bring about vasoconstriction.

The Postmortem Diagnosis

1. Encapsulated empyema, left.
2. Pulmonary tuberculosis with cavitation, left.
3. Diffuse acinous nodose tuberculosis, left.
4. Acute ulcerative tuberculosis of intestines, ileocolitis and appendicitis.
5. Tuberculous adenopathy, periaortic, abdominal and right supraclavicular nodes.
6. Suppurative sinusitis, involving right ethmoid, sphenoid, middle ear and mastoid cells.
7. Tuberculous meningitis.
8. Tubercles in liver and kidneys.

DISCUSSION

This far advanced patient was admitted for study in the spring, after a February activation. During the course of the first three months he revealed some improvement, that is, leucocytes and respiratory rate tended to decline while the blood pressure and weight increased. Alkalinization may, in part, have been responsible for this temporary improvement but it must be kept in mind that the season was favorable because of the rapid increase in environmental temperatures.

Clinical progression would appear to have been accelerated in midsummer when blood pressure crests occurred with two polar episodes.

After this, the pulse rate increased to a crest, pH declined and a febrile crest was observed.

On the whole, the comprehensive graph gives the impression that the patient was not particularly toxaemic or at least that the clinical reaction was not marked until the autumnal polar air masses swept over the city. With these the clinical focal reactions became evident:

(T) An alveolar ulceration, with tooth extraction on September 24. The augmentation of pain (swelling) with a major tropical air mass can be followed in the meteorogram.

(A) Sore throat and hoarseness on October 13, and a repetition **(B)** of this on November 16 (**(T)**, **(A)**, **(B)** on comprehensive graph).

The episodes of sore throat were both associated with the passage of major cold air masses and with increasing blood pressure.

Finally, either with or shortly before the 19th of December a general dissemination of bacilli must have occurred because terminal meningitis began. This period was associated with lower pH levels of the 14th, 15th and 16th of December. In addition, the blood pressure was low and a very striking increase in respiratory rate can be observed in the graph.

Finally the patient died on February 1 at a time when the blood pressure crest coincided with a major barometric crest.

When we follow the fluctuating meteorology of the time in selected and well defined polar episodes of the comprehensive graph labelled **(1)–(9)** it becomes evident that the passage of each cold air mass involved a phase of relative anoxia of the tissues (when the vascular bed tends to contract). This was in turn associated with a relative acidosis, and with this a decrease in resistance occurred. The tissues were first stimulated, finally fatigued as the vessels and capillaries became more permeable, as enzymes were liberated and as digestion was enhanced. Intoxication and dissemination were then accentuated.

TUBERCULOSIS SUBJECT 6—FAR ADVANCED CASE—FATAL TERMINATION

We finally study the companion patient to tuberculosis subject 5, who revealed a course that is comparable, although in this patient the date of the break in resistance was delayed a few weeks. The patient was of interest, too, presenting a series of clinical episodes that were associated with joint involvement.

The record concerned a colored male who was admitted to the Research and Educational Hospital on April 28, 1937 and died on January 18, 1938.

Clinical Record

The patient, R. B., was a colored male shoe tinter, admitted to the Research and Educational Hospital on April 28, 1937 with the history of an illness beginning in the spring of 1936, when he first noticed weakness, headaches and a gradual loss of weight with some muscular aches and pains.

By the middle of July, 1936, when he consulted a physician, he had lost 15 pounds. The physician prescribed salicylates and advised taking his temperature daily. He found that he was running a fever of 100° to 102°F. daily. In August, 1936 he began to take 40 grains of sodium salicylate daily. By the end of September the fever had subsided and he had gained 12 pounds. At this time he discontinued salicylates. In November, 1936 symptoms returned with fever up to 100°F., weakness, headaches and loss of weight.

In January, 1937 he began taking salicylates again without much improvement. In February he first noticed pain and stiffness of his left knee which have persisted.

Six weeks before admission, about March 15, 1937 **(1)** (text figure 22), his right elbow became swollen and sore. Three weeks before admission, about April 7 **(2)**, he noticed swelling and redness of the lateral surface of his left palm and swelling of the metacarpal phalangeal joint of the left index finger. He was admitted on April 28, 1937 **(3)**.

He had measles, mumps, chicken pox and pertussis as a child and gonorrhoea in 1932. He smoked 5 or 6 cigarettes daily and rarely used alcohol. His family history was essentially negative.

Physical examination revealed a fairly well developed but thin, colored male of twenty-nine who did not appear acutely ill. The head, eyes, ears, nose and oral cavity were essentially normal. The heart borders were within normal limits and the tones regular and of good quality. The chest was resonant to percussion and breath sounds were normal. The abdomen was flat. There were no masses or tenderness. The spleen and the lower pole of the right kidney were palpable. The genitalia were those of a normal male.

The extremities showed the following lesions: right upper extremity—a fluctuant mass over the extensor surface of the right forearm and a cystic mass, not tender, over the anterior portion of the right shoulder; left upper extremity—a fluctuant mass, 5 cm. in diameter, with necrotic centre in the thenar space and a swelling on the dorsum of the hand at the phalangeal metacarpal joint of the index finger; left lower extremity—a baggy swelling of the left knee especially over the medial aspect; the right lower extremity was negative. Rectal examination revealed a slightly enlarged and baggy prostate.

Laboratory tests showed the Wassermann and Kahn tests and urine to be negative. Haemoglobin was 9.7 g.; red cells, 4,380,000; white cells, 19,150; polymorphonuclears, 83 per cent; mononuclears, 11 per cent. Glucose was

72, CO_2 combining power was 49, and nonprotein nitrogen was 25. The sputum was negative.

His course in the hospital was as follows:

April 30, 1937: Abscess of left thenar area aspirated.

May 18: Abscess at right elbow aspirated. (Guinea pig inoculation positive for tubercle bacilli.)

June 15: Abscess over left sternoclavicular joint aspirated.

June 29: Abscess over right elbow aspirated.

July 4: 150 cc. of pus aspirated from abscess over anterior portion of chest.

July 15: Abscess over anterior chest has broken down and is draining.

September 5: Has developed abscess over dorsum of left foot.

November 2: Initial pneumothorax right.

November 4, 8, 10, 16, 21: Pneumothorax refills.

December 10, 18: Refills.

January 18, 1938: At 7 p.m. patient suddenly became semicomatose with twitching of arms and legs. There was marked rigidity of the neck and he did not respond to questions. He expired at 10:10 p.m.

Roentgenological examination made May 11, 1937 (roentgenogram 13) showed irregular densities in right upper lung and in left paravertebral region extending upward towards apex from hilum. Findings were consistent with tuberculous infiltrations. There were also small calcified areas in the hilum region which probably represent calcification in peribronchial nodes suggestive of an old hilum tuberculosis.

Examination made September 10, 1937 (roentgenogram 14) showed questionable extension of process in right upper lobe. Densities in left paravertebral region were less marked than on previous examination.

Examination made September 27, 1937 (roentgenogram 15) showed practically the same findings noted on previous examination.

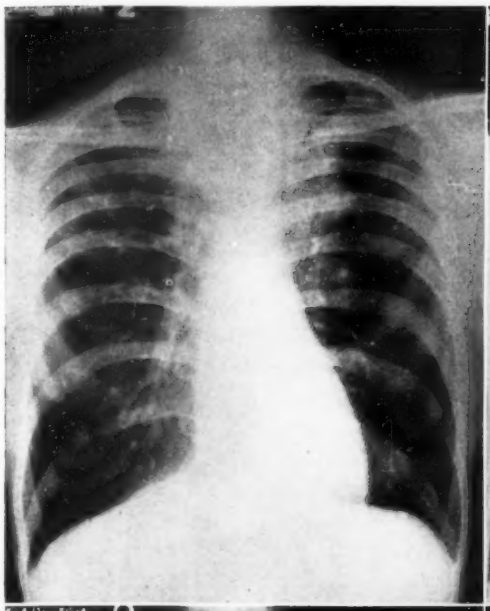
Examination made November 11, 1937 (roentgenogram 16) showed the right lung collapsed to about half the volume of the thoracic cavity on that side. As far as could be judged the densities within the collapsed lung were about the same as those on the previous examination. The left lung also showed practically the same findings as were noted on the previous examination.

Weather at the Time of Activation

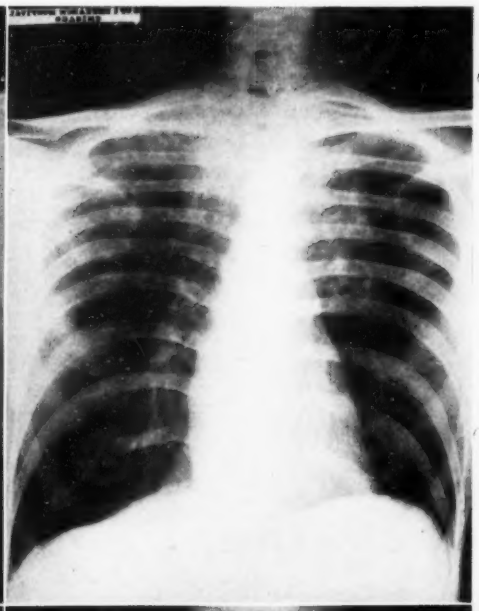
In this case activation began in the spring of 1936, that is, at a period following the severe cold of late January and February, and therefore under the same environmental circumstances as tuberculosis subject 5.

He first noticed headache and loss of weight. It is only possible to date the clinical changes relatively, because definite dates are not indicated in

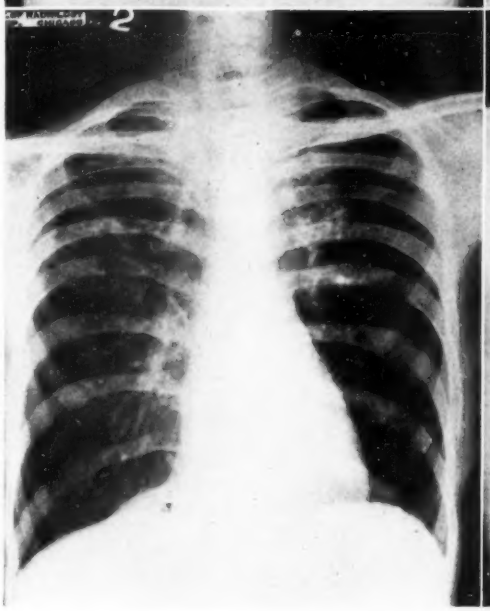
ROENTGENOGRAM 13. May 11, 1937



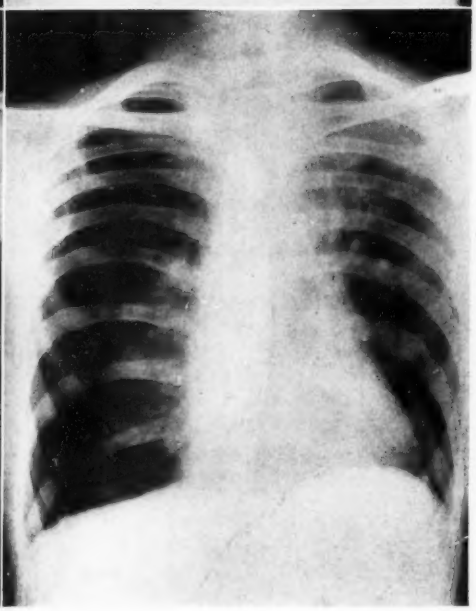
ROENTGENOGRAM 14. September 10, 1937

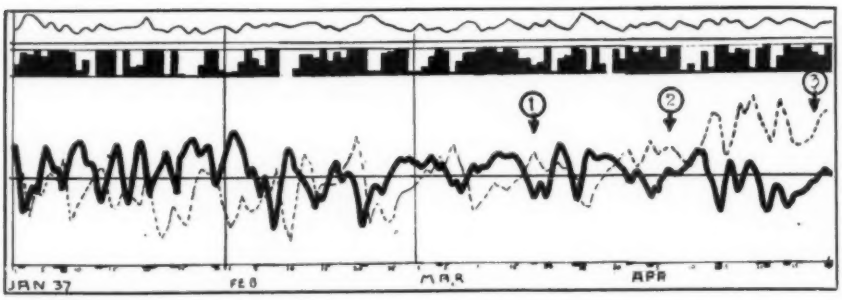


ROENTGENOGRAM 15. September 27, 1937

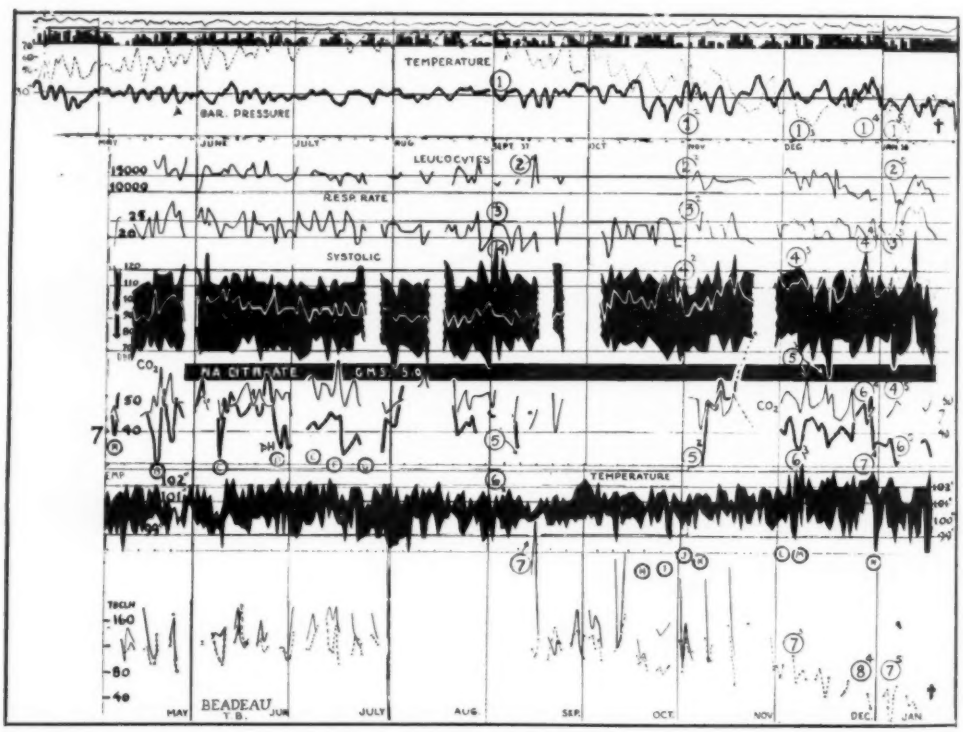


ROENTGENOGRAM 16. November 11, 1937





TEXT FIG. 22. Meteorogram to illustrate the clinical events in tuberculosis subject 6.



TEXT FIG. 23. Biometeorogram of tuberculosis subject 6. (See text for detailed description.)

the history, but in a meteorogram (text figure 22) the swelling of joints **(1)** and **(2)**, and admission to the hospital **(3)** are indicated.

The presumptive date of swelling of the elbow **(1)** occurred at a tropical crest when there was marked precipitation, and swelling of the fingers

(2) occurred when our preceding patient entered the hospital, while hospital admission **(3)** followed in the wake of the cold wave with a barometric crest.

The Biometeorogram

The biometeorogram (text figure 23) consists of a series of superimposed curves.

At the top the characteristic meteorogram followed by curves of total leucocytes, the respiratory rate, systolic and diastolic blood pressure, with pulse rate indicated as a white field. Then follow the CO_2 content and blood pH (heavy curve). Maximal and minimal temperatures are indicated; below this are the quantitative tuberculin reactions. Medication, consisting of 5 grains of sodium citrate three times a day, is indicated by the black bar, and death by the cross.

In this instance the periods of decreasing resistance are indicated by circled numbers **(1)**, **(1)**^{2}, **(1)**^{3}, **(1)**^{4} and **(1)**^{5} on the meteorogram, the first of these indicating the time of the approximate break which led to the fatal termination. The numbers below **(2)**, **(3)**, **(4)**, **(5)**, **(6)**, **(7)** etc. are related in the text to the different curves.

Clinical Notes

1937		
May	**(A)** 5	Pain
	10	Poor night; pain left knee
	11	Poor night; pain left knee
	12	
	13	
	14	Fever; slept poorly
	15	
	16	Mild diarrhoea
	17	
	18	
	(B)19	Joint pains; feels shaky
	27	Poor night
	28	Tired
	29	Began Na-citrate
June	4	Tired
	5	Poor night
	6	Very poor day
	7	
	8	Tired
	(C)9	Tired; poor night
	10	Tired; precordial pain
	11	
	12	
	13	
	14	Restless night
	15	Tired
	16	Night sweat
	17	Poor night
	18	
	19	
	20	Restless night
	21	Tired
	22	Poor night
	23	Tired
	(D)30	Poor night; right sternoclavicular pain
July	7	Poor night
	(E)8	Poor night; abscess, right sternoclavicular area, ruptured
	9	Poor night
	10	
	11	Tired
	12	Tired
	(F)15	Tender left foot
	20	Poor night
	(G)24	Abscess left knee ruptured
	28	Poor night
	29	Drowsy
Sept.	19	Poor night

	20	Tired; nausea; emesis
	21	
	22	
	23	Nausea
	24	Poor day and night
	25	Tired
	26	Bad p.m.
Oct.	1	Tired
	2	
	3	Weak and tired; night sweat
	10	Codliver oil dressings left knee
	11	
	12	
	13	Poor night
	14	Poor night; tired
	15	
	16	
	17	Poor day
	18	
(H)	19	Pain left sacroiliac
	20	
	21	
	22	Restless night
	23	Tired
	24	Poor night
	25	Poor night
(I)	26	Tired; nausea; pain left hip worse
	27	Tired
Nov.	1	Poor night; chilly
(J)	2	Tired; initial pneumothorax left chest
	6	Poor night
	7	
	8	Very poor night
(K)	9	Tired; pain left knee
	13	Shaky; subjective fever
	14	Shaky; subjective fever
	15	
	16	Poor night
	17	Tired
	18	Tired
	19	Very poor night
	20	Very poor night
	26	Tired; right hand numb and weak
	27	Poor night
	28	Poor day
	29	Poor night
	30	Poor night; tired
Dec.	2	Tired
(L)	3	Tired
	4	Tired
	5	Sharp pain right arm
	6	Poor night
(M)	10	Abscess ruptured right ankle
	14	Poor night
	15	Tired
	19	"Dopey"; subjective temperature
	20	Diarrhoea
(N)	29	Soreness right sternoclavicular
1938		
Jan.	3	Pneumothorax refill
	4	Dyspnoea; poor night
	5	Dyspnoea; tired
	6	Dyspnoea
	7	Dyspnoea
	8	Dyspnoea
	9	Dyspnoea; poor day; subjective fever
	14	Poor night; draining sinus left first finger
	15	
	16	Dizzy spell; bad day
	17	
	18	Expired 10 p.m.

Analysis of Curves

When we examine the curves it will be noted that the first break could be dated approximately to early September, 1937 and this has been indicated by the period marked **(1)** in the graph, when a polar front passed on September 2.

Environmental temperatures had been quite high and barometric pressures low and there was rain on the 1st and 2nd of September.

When we examine the curves it will be noted that at this time a blood pressure crest was reached **(4)**. With this the respiratory rate increased, the blood pH declined to a low level on the 10th **(5)**, the afternoon tem-

peratures increased to the 6th **(6)** and finally on the 16th of the month we find an unusually wide flare-up of the tuberculin reaction. Stimulation of the bone marrow, shown in a leucocytic crest, was evident on the 14th of the month **(2)**.

Up to this time the fever had been held at a fairly constant level. By the end of September a distinct rise was evident. Unfortunately our observations at this time were fragmentary.

Episode **(1)**[2]: With the 1st of November we have another period of stimulation (and fatigue). A barometric crest was reached, temperatures fell to a low on the 3rd. Leucocytic stimulation was evident on the 4th **(2)**[2], respiratory rate increased on the 6th **(3)**[2], but a low pH was also recorded **(5)**[2]. This time only a minor blood pressure crest was in evidence **(4)**[2], characteristically the diastolic pressure revealed definite lows (fatigue). From this period on temperatures increased progressively. As in the preceding patient a sudden rise in blood pH occurred at this time and with it blood pressure levels increased. Now followed a sharp environmental decline with crests on the 20th of November and 10th of December.

Episode **(1)**[3]: Leucocytes were transiently stimulated but declined toward the end of December.

Blood pressure rose to a high of 122 mm. **(4)**[3], but again it is the decline that now dominated the picture **(5)**[3]. (Note the all-time low 92/54 on the 16th of December, to be discussed in connection with bacillary dissemination). CO_2 was transiently increased during this phase. A low pH **(6)**[3] was observed with a coincident febrile crest and the tuberculin reaction **(7)**[3] began a steep decline.

Episode **(1)**[4]: With the end of December we have a barometric crest **(1)**[4] and with it an agonal struggle to increase the blood pressure **(4)**[4]. The pH increased to a crest **(6)**[4], but with the decline to a low pH the body temperature fell sharply. The tuberclin reaction declined continuously **(8)**[4].

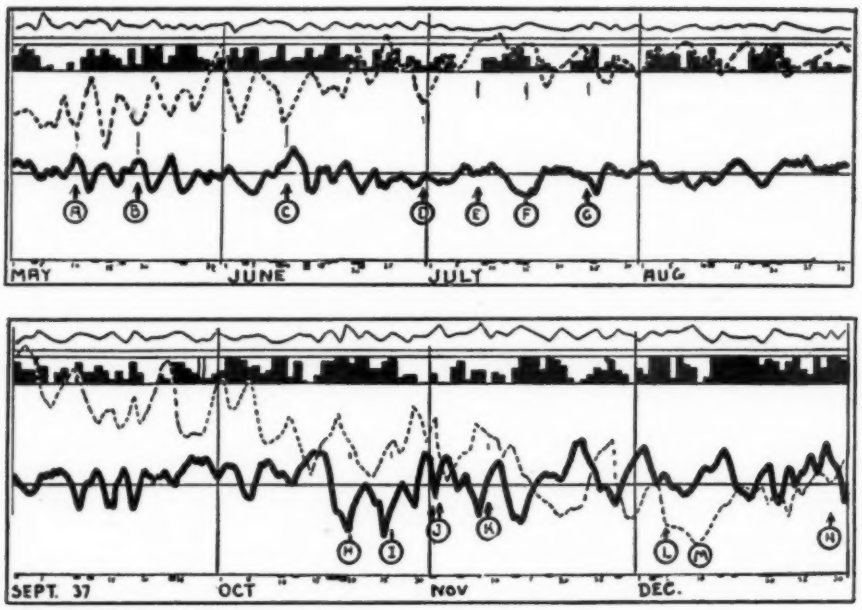
Episode **(1)**[5]: With the succeeding cold wave **(1)**[5] the respiratory rate **(3)**[5] now increased as did the pulse rate. The pH declined **(6)**[5] further as did the tuberculin reactivity **(7)**[5].

One final pressor crest was achieved on the 11th. The patient evidently felt a little better at the time, there were no complaints recorded. Then came the final collapse—"poor night," "dizzy spell"—and death with the succeeding barometric crest.

Final subjective clinical observations relating to the joint disturbance

of the patient have been lettered **(A)**–**(N)** over the temperature curve and the curve of the tuberculin reaction:

(A) May 10: Poor night, pain in left knee.
(B) May 19: Joint pain, feels shaky.
(C) June 10: Precordial pain.
(D) June 30: Right sternal clavicular joint pain.
(E) July 8: Abscess of the left clavicular joint ruptured.



TEXT FIG. 24. Meteorogram for the periods of clinical episodes lettered **(A)**–**(N)** for tuberculosis subject 6.

(F) July 15: Tender left foot.
(G) July 24: Abscess, left knee ruptured.
(H) October 19: Pain in left sacroiliac region.
(I) October 26: Left hip pain worse.
(J) November 2: Pneumothorax induction.
(K) November 9: Pain in left knee.
(L) December 5: Pain in right arm.
(M) December 10: Abscess, right ankle ruptured.
(N) December 29: Pain in sternoclavicular joint.

If we examine the first seven episodes, involving either pain or rupture (**(E)**–**(G)**) of abscesses, reference to the pH curve immediately above and

identified by similar letters will indicate the characteristic coincidence of subjective symptoms with low pH levels.

This is again to be observed with episodes **(K)**, **(L)**, **(N)** during November and December. Obviously we are here dealing with the COD phase, when, after anoxia, tissues swell and pain will become more evident.

The relation to the meteorological status at the time of these episodes **(A)**–**(N)** is made apparent in text figure 24.

A mere inspection of the meteorogram shows that in all instances except those when there was rupture of the abscesses (**(E)**–**(G)**) there is a distinct association with fall in temperature, which has preceded the pain from twenty-four to forty-eight hours.

Rupture has occurred with rising temperatures when peripheral dilatation of the vascular system has accentuated a COD phase.

The Postmortem Diagnosis

1. Generalized miliary tuberculosis.
2. Multiple superficial soft tissue abscesses and ulcerations.
3. Tuberculous involvement of the sternoclavicular joint, right, and of the second metacarpal-phalangeal joint.
4. Contraction deformity of both hips and knees.
5. Marked congestion of the liver and kidneys.
6. Hydrothorax, bilateral.
7. Hydropericardium.
8. Moderate ascites.

DISCUSSION

In this companion case to tuberculosis subject 5 we deal with widely disseminated tuberculous processes (multiple joint and subcutaneous abscesses) together with pulmonary involvement and terminal miliary dissemination in a young colored male. The patient was given citrate in large doses and this may have had some influence in prolonging the course of the disease; in addition pneumothorax was instituted but there was continuous progression of the disease.

Nevertheless the episodic effect of major weather disturbances can be readily followed and we have discussed these effects in broad outline as episodes **(1)**[1], **(1)**[2], **(1)**[3], **(1)**[4], **(1)**[5] and in addition the reflection in the joint symptomatology can be readily followed in the associated meteorogram.

Of particular interest is the fact that the lowest level of the diastolic

blood pressure (December 16) coincided with the period of presumptive bacillary dissemination in our tuberculosis subject 5 and the same episode was probably associated with the bacillary dissemination evident as a final miliary tuberculosis in this patient, both phenomena being related to the early December cold wave, shown in the comprehensive meteorogram.

COMMENT

In these 6 cases we have been able to demonstrate that periods of biological fatigue, characterized by a well defined bio-physico-chemical and clinical status and initiated by changes in the air mass in which the patient lives, are followed by activation and spread of the tuberculous process. Paradoxically a similar air mass (that is, the passage of polar interfaces) may, under certain conditions, be followed by improvement.

The recognition of this simple pendulation will, we believe, be useful in the interpretation of the clinical course of pulmonary tuberculosis.

The biological status of the tissues is constantly maintained in an unstable equilibrium between two poles: (*a*) on the one hand, a trend toward anabolism, toward lessened cellular (and endothelial) permeability, lessened secretion, dehydration, the accumulation of buffers, as well as toward a higher pH level of the venous blood, a lessened production of CO_2, a lessened production of polymorphonuclear leucocytes in comparison to the lymphocytes, a higher sugar level, a higher blood pressure level, etc.

In general this corresponds to a relative sympathicotonia, though it actually has a much broader basis than merely the endocrines. Actually every physiological mechanism is involved.

During such a period, inflammatory as well as tissue digestive phenomena tend to be suppressed, bacterial dissemination is lessened, absorption, and, with it, intoxication, is diminished, clinical comfort is more pronounced.

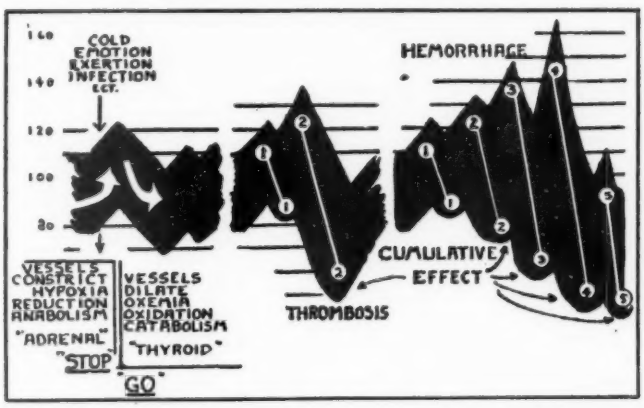
An exaggeration of this status may at times carry with it greater liability to haemorrhage and increased cough, the first because of increase in blood pressure, the second because of the tendency to dehydration. Weight (apart from water retention) tends to increase, while fever tends to diminish (though the morning temperatures may be raised). The sputum volume diminishes.

(*b*) The opposite phase is one characterized by increasing catabolism and increased cellular (and endothelial) permeability; an increase in

secretion, in hydration (the blood may become more concentrated); loss of buffers, vitamins, minerals, etc.; a relatively low pH of the venous blood; increased production of CO_2; polymorphonuclear leucocytic activation; a lower sugar level and a lower blood pressure level.

This conforms in general to a vagus or "parasympathetic" status. Inflammatory processes are enhanced, digestion and necrosis speeded, exudative processes are pronounced, bacterial dissemination favored and clinical symptoms aggravated. There is more pain (tissues swell), greater fatigue, more discomfort.

When exaggerated, this status forms the basis for exacerbation or activation of disease and with it fever rises, the sputum is increased, the



TEXT FIG. 25. Schematic blood pressure reactions to environmental change. Simple and cumulative effect.

tendency toward haemorrhage, cavity formation, pleural penetration and bacterial dissemination is accentuated by the digestive phenomena.

Every environmental demand on the organism brings about a greater or lesser disturbance of the balance, the more pronounced the demand, or the more labile the patient or the focus, the greater the clinical reflection.

We can follow the definite step-like shift in the condition with every major change in the air mass, if we observe clinical episodes or if we merely inspect the blood pressure curve, the leucocyte curve or the respiratory rate.

Each increase in systolic and diastolic blood pressure is followed by a phase of augmented decline, in the nature of the theoretical curve indicated in text figure 25. Here the environmental impact (cold or an equivalent such as emotional excitation, exertion, infection, etc.) is asso-

ciated with a relative sympathicotonia, followed by a sharp decline which may reach fatigue levels and which may be cumulative in character, as indicated in the third portion of this diagram where the progression of impacts **(1)**, **(2)**, **(3)**, **(4)** and **(5)** is ultimately followed by unusually low diastolic blood pressure levels.

Every disturbance of balance has inherent in it two possibilities, that is, clinical improvement or clinical harm, the final outcome (leaving out of consideration the matter of bacterial proliferation) depending on the preceding state of tissue balance, on availability of supplies of buffers and of energy stores as well as on the state of the circulatory mechanisms. Given adequate buffer and energy supplies, and moderate pendulation after an energy impact, the passage of a cold air mass would appear to enhance and build up the first phase, that is, the anabolic, inhibitory or recovery group of mechanisms. But given a situation when buffers are exhausted and energy supply is low (sugars, fats, proteins, vitamins, iodine, calcium, etc.) each energy impact is followed by an exaggeration of the catabolic phase and the more pronounced the impact, the more rapid and extensive the break in resistance.

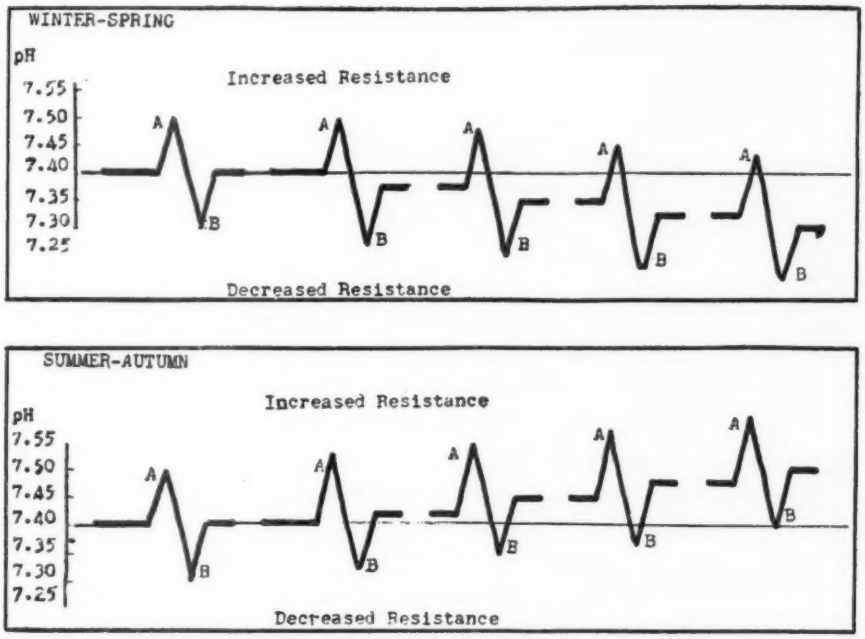
The term resistance, when used in connection with the clinical picture of pulmonary tuberculosis as here portrayed, hinges largely on a biochemical and physiological tide which has its ebb in the late winter and spring and its flood stage in the autumn. In the spring the organism is not only depleted of vital stores, the situation is complicated because environmental variability is at its maximum and each passage of a cold air mass (with its associated anoxia, followed by a relative acidosis) pushes down the resistance levels. In the autumn, even with stores reëstablished (by the meteorological quiescence of summer, an alkalotic trend in the diet and the effect of sunshine and warmth) the organism becomes peculiarly susceptible to environmental swings[3] and meteorological turbulence occurring in the late summer and autumn may break through the protection which the accumulation of stores has provided. At this season the passage of cold air masses, which in the normal individual results in the accentuation of well being, may be portentous for the tuberculous individual.

Graphically we can express this pendulation in text figure 26 where the biological status is merely expressed in terms of pH levels of the venous blood.

[3] This has been observed in an entirely different biological field, namely, by Bodine, Allen and their associates (12) in work on the diapause occurring during the development of the grasshopper embryo.

A series of environmental impacts that swing the biological reactions in a characteristic pendulation **(A)–(B)** here ultimately result in a decline in the level of the base line until the final low of 7.3 is indicated. This would correspond to the effects observed in the late winter and spring.

On the other hand similar impacts in other individuals and at other seasons, for instance, summer and autumn, may result in the attainment of a higher level, in this instance indicated at 7.5 with presumably a resulting increase in resistance.



TEXT FIG. 26. Graphic representation of resistance pendulation with energy impacts as reflected in the pH levels of the venous blood.

The major alkalotic crests observed in our patients studied while on an alkaline regimen revealed the accentuation of a characteristic "stop" or ARS phase, but despite this artificially achieved enrichment, periods of unusually low pH almost invariably followed, and with this bacillary dissemination occurred. (The animal experiments designed to illustrate this point will be reported separately by Doctor Howe.)

Resistance, though many sided are the processes involved, is, as we survey the findings in these advanced cases, primarily conditioned by the meteorological situation, and this is the reason for the great trend toward

activation in the late winter and spring, for the relative quiescence of summer and early autumn, as well as for the occasional reactivation of cases with early autumnal meteorological turbulence.

Fundamentally the same mechanisms are involved when we consider the relation of resistance to habitus. The broad (pyknic) anabolic type is generally more resistant, with fibrotic phenomena accentuated, in comparison to the slender and more catabolic type. In the latter group, however, we find the same paradox that we have already discussed. The slender individual, biochemically more labile and physically more susceptible to the environment because of deficient skin buffering, handles tuberculous infection by an exaggeration of two diametrically opposite pathways; the speed of defensive mechanisms (agglutinative, digestive, etc.) may readily and completely overcome minor doses of bacilli, making the individual less susceptible. That same speed and vigor of the reaction, however, may, because of the general tendency of individuals of this type to enhanced catabolism and fatigue, result in rapid progression of an infection that has once been established.

Finally we would call attention to the possible enhancement of resistance when the subject is properly alkalinized, or chemically buffered in a variety of ways. We have simply made use of sodium citrate in large doses. One of us (2) called attention to this possibility years ago but in connection with it pointed out that the very evidence of improvement (decreased temperature, monocytic shift, lessening of sputum, increase in blood pressure) carried with it some risk, particularly in haemorrhagic cases where an increase in blood pressure might result in accentuating the trend to haemorrhage.

While striking results can hardly be expected in far advanced cases of the type that we have here presented, only careful study of less advanced cases can determine a possible usefulness.

SUMMARY

Of all the clinical phenomena observed in the progression of tuberculous disease in the human, the recognition of the seasonal activation of the disease (evident in the usual clinical findings, in complications and finally in death) is most ancient, as well as universally accepted.

For the patient who has established a *modus vivendi*, it is the late winter and spring that is often associated with renewed signs of activation (tuberculin reaction, loss of weight, increase of fever, leucocyte count and sputum output, etc.). This particular study is primarily concerned with the examination of this phenomenon.

By season we merely express the sum total of continued weather effects. When we broadly consider weather effectors as they concern the human we can think largely in terms of the energy requirement for adjustment. Here the frequency of the change, the relative degree of change, the extremes involved, are all of significance. For purposes of simplicity we have limited the consideration largely to the effect of cold.

The passage of a cold air-mass over a region is associated with a relative sympathicotonia in the population and this is followed by a relative vagotonia; to use chemical equivalents it is associated with a relative alkalosis followed by a relative acidosis. In terms of the blood pressure, a period of vascular spasm and increased systolic and diastolic blood pressures is followed by a reversal to lower systolic and diastolic blood pressures; there is first contraction of the peripheral vascular bed (the organism tends to shut itself off from the environment!) and this is followed by a relative peripheral dilatation.

In the first stage the capillary bed is less permeable, in the second, more permeable; in the first stage there is a relative lymphatic overbalance, in the second a myeloid overbalance.

This meteorologically induced biological pendulation of all physico-chemical and physiological overbalances must affect tuberculous foci. The younger and more labile the focus, the more poorly encapsulated, the greater will be the reactivity to weather (and seasonal) change; the older and more stable the lesion and the more encapsulated, the less will be the effect of these physiological and patho-physiological alterations.

The effect of biological pendulation will in general be as follows: With the first phase, resistance to tuberculous dissemination and progression will be increased. That is, with lessened permeability and lowered metabolism, increased alkalinity and with relative lymphocytosis, as well as dehydration, the tendency to bacillary dissemination will be decreased, tissue digestion and breakdown reduced, intoxication lessened and clinical improvement becomes evident. With the second stage this picture is completely reversed.

With every energy impact (we are here limited to the consideration of weather effects, but all extraneous changes affecting the body must be considered) initiating such biological pendulation, the clinical outcome will depend on the net result, that is, on the attainment of a biological milieu of greater anabolic potential (beneficial) or greater catabolic potential (that is, harmful). Here obviously the available reserves (foodstuffs, vitamins, buffers, endocrines, etc., as well as the local cellular situation) will provide the background and condition the ultimate result.

In the 6 far advanced cases here used to illustrate this situation, day-by-day studies were carried out over long periods of time (the longest over nine months) and the biochemical and clinical tide was studied in relation to the meteorological environment of the time. The tests included blood pH, CO_2, cholesterol, the cell count, quantitative tuberculin reaction as well as oxidative potential of the skin, blood pressure, sputum volume, blood cultures with daily inoculation of guinea pigs, etc.

From these observations and those previously published we can draw the following conclusions:

(*1*) The trend to activation of tuberculosis observed in the late winter and spring is associated with the general tendency to increased catabolism evident in normal individuals as well as patients studied. The lowering of the blood pH (relative acidity) and of the blood pressure (vascular and general cellular fatigue) along with the increase in capillary permeability give objective evidence that resistance to tuberculous extension decreases with organic (tissue) fatigue. This organic fatigue results from the loss of buffers, vitamins and essential mineral and organic constituents, incidental to the repetition of environmental impacts of the severe meteorological turbulence of the late winter and spring. Basically it must be considered from the point of view of an energy deficit.

(*2*) On the other hand, an objective increase in resistance occurs with release from the meteorological strain in the summer and autumn, with increase in blood pressure, increasing pH, lessening of permeability of the capillaries, etc.

(*3*) Every meteorological change, particularly the passage of clearly defined cyclonic fronts, finds reflection in a changed biochemical status of the normal as well as the tuberculous individual. Since this reaction is diphasic, it may result in either harm or benefit to the individual who is ill, depending on many adventitious factors, that is, the preceding state of the patient, the availability of reserve, the condition of the individual foci, the hormone balance (particularly the sex cycle), etc.

(*4*) It was demonstrated that an identical environmental situation that is reflected in the death of one patient may be associated with a beneficial change in the organic phase in a second patient.

(*5*) Experimental alkalinization of the patient (all far advanced cases) apparently results in some increase in resistance to tuberculous infection.

SUMARIO

De todos los fenómenos clínicos observados en la evolución de la enfermedad tuberculosa en el hombre, el más antiguo, y universalmente

aceptado, es el reconocimiento de la activación estacional de la enfermedad (manifiesta en los habituales hallazgos clínicos, en las complicaciones y por fin en la muerte).

Para el enfermo que ha establecido un *modus vivendi*, la útima parte del invierno y la primavera son las que se asocian más a menudo con signos de reactivación (positividad a la tuberculina, pérdida de peso, aumento de la fiebre, leucocitosis, secreción de esputo, etc.). El estudio actual está dedicado primordialmente a un análisis de este fenómeno.

Por estación se sobrentiende meramente la suma total de los continuos efectos del clima. Cuando consideramos ampliamente los factores meteorológicos en lo que afectan al hombre, podemos considerarlos en gran parte en términos de los requisitos de energía para ajuste orgánico. De ahí que revistan importancia tanto la frecuencia como la relativa intensidad de los cambios y los extremos que éstos alcancen. Para mayor sencillez, se ha limitado este estudio en gran parte a los efectos del frío.

El paso de una masa de aire frío sobre una región se asocia con una simpaticotonía relativa en la población, que va seguida de una vagotonia relativa, o empleando equivalentes químicos, se asocia con una alcalosis relativa seguida de una acidosis relativa. En términos de tensión sanguínea, un período de espasmo vascular y de hipertensión sistólica y diastólica va seguido de una baja de la tensión, tanto sistólica como diastólica; al principio se presenta contracción de la red vascular periférica (el organismo tiende a aislarse del ambiente) y esto va seguido de una dilatación periférica relativa.

En el primer período la red capilar es menos, y en el segundo más permeable; en el primero existe un equilibrio hiperlinfático relativo; en el segundo equilibrio hipermieloideo.

Esta oscilación biológica de todos los hiperequilibrios fisioquímicos y fisiológicos, provocada meteorológicamente, debe afectar los focos tuberculosos. Mientras más recientes y más lábiles y peor encapsulados éstos, mayor será la reactividad a las alteraciones meteorológicas (y estacionales); y mientras más antiguas y estables, y más encapsuladas las lesiones, menor será el efecto producido por dichas alteraciones fisiológicas y patofisiológicas.

El efecto de esta oscilación o pendulación biológica será en general el siguiente: En la primera fase, aumentará la resistencia a la diseminación y evolución de la tuberculosis; es decir, disminuídos la permeabilidad y el metabolismo, acrecentada la alcalinidad y con linfocitosis relativa, así como deshidratación, disminuirá la tendencia a la diseminación bacilar, descenderán la digestión y desintegración histológica y la intoxicación,

y se pondrá de manifiesto la mejoría clínica. En el segundo período se invierte completamente este cuadro.

Con cada choque de energía iniciado por dicha oscilación biológica (nos limitamos a la consideración de los efectos meteorológicos, pero hay que tomar en cuenta cuanta alteración extrínseca afecte al organismo), el desenlace clínico dependerá del resultado neto; es decir, de la obtención de un medio biológico de mayor potencial anabólico (beneficioso) o catabólico (nocivo). Aquí también las reservas disponibles (alimentos, vitaminas, amortiguadores, endocrinas, etc., así como la situación celular), establecerán el fondo o terreno y condicionarán el resultado definitivo.

En los 6 casos muy avanzados utilizados aquí para ilustrar la situación, se llevaron a cabo estudios diarios durante períodos prolongados de tiempo (el máximo más de nueve meses), y se estudió la evolución bioquímica y clínica en relación con el ambiente meteorológico en el período dado. Las pruebas comprendieron: pH de la sangre, CO_2, colesterina, hematimetría, reacción cuantitativa a la tuberculina así como potencial oxidante de la piel, tensión sanguínea, volumen de esputo, hemocultivos con inoculación en el cobayo, etc.

De estas observaciones y de otras previamente publicadas, cabe sacar las siguientes conclusiones:

(*1*) La tendencia a la activación que se observa en la tuberculosis a fines del invierno y en la primavera, se asocia con una tendencia general a un hipercatabolismo observado en los sujetos normales así como en los enfermos estudiados. La baja de la pH sanguínea (acidez relativa) y de la tensión sanguínea (fatiga vascular y celular general), junto con la hipermeabilidad capilar, ofrecen pruebas objetivas de que la resistencia a la diseminación tuberculosa disminuye con la fatiga orgánica (histológica). Esta fatiga orgánica proviene de la pérdida de amortiguadores, vitaminas y de los componentes minerales y orgánicos esenciales que es incidental a la repetición de los choques ambientales producidos por la intensa turbulencia meteorológica que se presenta a fines del invierno y en la primavera. Básicamente, hay que considerar esto como equivalente a un déficit de energía.

(*2*) En cambio, obsérvase un aumento objetivo de la resistencia al cesar la tensión meteorológica, en el verano y otoño, y aumentar la tensión sanguínea y la pH, y disminuir la permeabilidad capilar, etc.

(*3*) Toda alteración meteorológica, y en particular el paso de frentes ciclónicos netamente definidios, se refleja e una alteración del estado bioquímico del sujeto normal, así como tuberculoso. Como dicha

reacción es bifásica, puede resultar nociva o beneficiosa para el individuo enfermo, dependiendo esto de muchos factores adventicios, como son es estado anterior del enfermo, la disponibilidad de reservas, el estado de lol focos individuales, el equilibrio hormónico (en particular el ciclo sexual), etc.

(*4*) Se ha demostrado que una situación ambiental idéntica que en un enfermo se refleja en la muerte, en otro puede asociarse con una alteración beneficiosa en la fase orgánica.

(*5*) La alcalización experimental del enfermo (en los casos muy avanzados) aparentemente obtiene algún aumento en la resistencia a la infección tuberculosa.

Opportunity for the pursuit of further detailed studies of this nature not being possible for us at the University because of administrative action, the observations here published must conclude our excursion into this particular field. I have the hope that both of my associates, Professor J. S. Howe of the Department of Pathology of the Medical College of Virginia and Mrs. M. E. Milliken, now with the Mills Laboratory in Tampa, Florida, who carried out all the clinical determinations, may find more encouragement in their present positions. The studies of Professor Howe on bacterial dissemination, which were carried out in these patients as well as in animals, will be published later.

W. F. P.

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DECOMPRESSION OF TUBERCULOUS CAVITIES[1]

A Skin Flap Operation for Residual Cavities following Thoracoplasty

S. J. SHIPMAN,[2] W. L. ROGERS AND A. C. DANIELS

In recent years upper stage thoracoplasties have been used with success in the treatment of tuberculous cavitation. Nevertheless, in the hands of most operators, a certain small number of cavities have remained unclosed in spite of what appeared to be adequate collapse. To meet this problem various modifications of standard thoracoplasty technique have been devised, such as freeing the apex (Semb), removing the transverse processes and anterior stages with removal of the costal cartilages. Even after the most extensive decostalization or mobilization of the lung a few cavities remained as slit-like or ovoid holes, to serve as the source of 1 or 2 cc. of positive sputum. Unfortunately the more extensive operations at times seemed to produce complications, such as atelectasis and extension of the tuberculous disease and, in some patients, mechanical difficulties due to decreased respiratory reserve.

Up to the present time the usual surgical approach, based as it is upon the concept that tuberculous cavities are merely vacant spaces hollowed by disease from the surrounding lung, neglects the newer knowledge of cavitation. Eloesser (1, 2), in his classical work on bronchial stenosis especially as it relates to tuberculosis, and Coryllos and Ornstein (8), as well as Pinner and others have pointed the way toward a dynamic concept of cavitation. This recognizes that the bronchial tree as well as the surrounding lung is not static, but expansile and that the air passages themselves expand on inspiration and contract on expiration. In a diseased and tortuous condition such bronchi allow air to enter but make egress of air and secretions extremely difficult. A one-way check valve is formed, blowing up, as it were, small breaches in the lung structure until they become clinically recognizable cavities. These are spherical and have been termed tension or blocked cavities. They are now recognized to offer the most stubborn resistance to the usual collapse measures.

[1] Presented before the Medical Section at the 37th annual meeting of the National Tuberculosis Association, San Antonio, Texas, May 7, 1941.

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It is thus seen that a modern concept of tuberculous cavitation requires that two factors be kept in mind: (*1*) the *intrinsic* or bronchial factor leading to the one-way valve and consequent high intracavitary pressures, and (*2*) the *extrinsic* or chest wall factor which sooner or later operates by adhesions to keep the cavity open as long as the chest wall maintains its normal position. It is the latter that has been attacked so successfully by orthodox collapse measures, but it is also the latter that fails *alone* to close all cavities when used without regard to the intrinsic, bronchial or high pressure factor.

Experiments with needles and rubber tubes of various sizes in some of the tension cavities which have come under our observation have shown that simple exposure to atmospheric pressure will cause such a cavity to disappear in a few minutes and that it will promptly reappear when the needle or tube is withdrawn. One of us (Rogers) has needled and sucked the air from such cavities immediately prior to thoracoplasty and watched them disappear. Following thoracoplasty he has seen them remain closed in some cases and reappear in others. Monaldi (7) has apparently cured cavities by the insertion of a catheter followed by suction, but in our hands this procedure has commonly failed, especially in large cavities (as Monaldi himself says), probably due to the fact that the intrinsic factor was controlled in these cases but the extrinsic was not. Certainly in our hands the suction method has failed to close the type of cavity under discussion. This is the reverse of the extensive and variously modified thoracoplasties which have failed because the extrinsic factor was controlled but the intrinsic was not.

The ideal approach has seemed to us to be a consecutive attack directed at both intrinsic and extrinsic factors; and since the orthodox approach begins with thoracoplasty (in the absence of a satisfactory pneumothorax) the operation has begun with this procedure. In all cases a routine upper stage thoracoplasty was done with the resection of all of the first and second ribs and a liberal segment of the third, using the cautery to destroy the periosteum, the remaining periosteal beds being touched with 10 per cent formalin. Further resection of the fourth and fifth ribs was then carried out at a later stage or in still later stages the sixth and seventh ribs and part of the scapula, if it seemed advisable, were resected.

Here it should be said that there may be some criticism of such conservative thoracoplasties. However, we should like to say that these procedures have been carried out in a small private institution where

the patients were well known to each other and where a bad result would have had lasting repercussions on patients' morale. From 1936 to 1940, 60 patients were operated upon in this manner in this institution. Up to the present time 40, or 66.6 per cent, are well and at work (including housework in the case of women) with negative or no sputum. The years 1940 and 1941 have not been included, the time elapsed since their thoracoplasties being too short to include them in the "at work group." Of the first 100 cases (including 1941), 4 have had residual cavities after thoracoplasty and have been judged suitable for the procedure to be described. It would therefore seem that with conservative thoracoplasty about 4 per cent of cases would have residual cavities and be candidates for drainage decompression.

Until recently, open drainage of tuberculous cavities has been almost uniformly disappointing. Nevertheless several authors have reported a few successful cases. Nissen (3) has reported successful drainage of a large anterior apical cavity following an unsuccessful attempt at plombage. In this case a muscle flap was used to fill the cavity space. Lilienthal (4) in 1927 described a case of open drainage of a secondarily infected tuberculous cavity which had been blocked-off following thoracoplasty. The fistula closed spontaneously and the patient remained well four years after operation. In 1929 Lilienthal (5), in discussing direct drainage of tuberculous pulmonary cavities, emphasized the following indications:

1: Virulent mixed infection with clinical signs of pulmonary abscess.
2: Those in which cavity collapse could not be obtained without great danger to life, and in which the accompanying sputum was so abundant that it continually threatened to cause bronchogenic extension.

Lilienthal also mentioned external and intrapleural drainage, and pointed out the importance in these cases of ascertaining the source of the sputum before operation. He cited 3 cases, 2 of which he had drained following thoracoplasty with temporary improvement. However, due to wound closure the cavities later reopened. In the third case the cavity was drained into an existing empyema, with resultant conversion of sputum. In 1931 Lilienthal (6) again mentioned this subject in discussing the operative treatment of pulmonary tuberculosis and recommended the use of a muscle flap to obliterate the residual cavity. However, the 2 cases cited had not been entirely successful.

It has seemed to us that the bad results of cavity drainage could be

accounted for very largely by the absence of adequate X-ray studies and an inadequate understanding of the dynamics of cavitation.

Four per cent of cavities remain open beneath conservative thoracoplasties. With the knowledge that such cavities, at least if of the tension type, tend to disappear if the pressure in them is maintained at an atmospheric level or less, *even during the exertion of cough, movement and so forth,* it was necessary to devise a method to open permanently such cavities until they could heal. It was believed that a skin flap sutured directly to the cavity wall (which in most cases meant a thick pleura as well as cavity wall) in the manner described by Eloesser for the treatment of empyema would most satisfactorily answer the purpose. Since the indication for the operation as well as the procedure itself may be best understood by an example, the first case is now described in some detail.

CASE REPORTS

Case 1: A white male dentist, thirty years of age, was first seen by Dr. Philip H. Pierson in August, 1938. He had had pleurisy with effusion on the right side in 1937. Because of infiltration and cavitation in the base of the right upper lobe, Doctor Pierson induced a pneumothorax, which compressed only the right base and was therefore abandoned. The sputum remained positive, the blood sedimentation test was 25 mm. in an hour (Cutler method) and the patient was referred to the Tuberculosis Division of the Ross General Hospital by Doctor Pierson on September 8, 1938. He remained febrile and the area of infiltration and cavitation became progressively larger. It was therefore decided to do an upper-stage thoracoplasty in the manner previously described, which was done December 16, 1938. The cavity increased rather than decreased in size. A second stage, taking the unremoved portion of the third rib and portions of the fourth, fifth, sixth and seventh ribs, was done January 26, 1939. The right upper lobe now seemed to be one large cavity and the chest wall did not fall in as might have been expected; it appeared to be held out in its normal position almost as though no thoracoplasty had been done. Suspecting that this was due to a high intracavity pressure, we needled the cavity, getting pressure readings of +12, +20 cm. of water on numerous occasions. If the needle was inserted into the cavity and left in place, the cavity seemed to disappear, only to appear again when the needle was withdrawn. The needle was left in the cavity for a month and the cavity reappeared when it was withdrawn. On June 5 a T-tube was placed in the cavity, the latter promptly disappeared, but the tube upset the patient and it was removed on July 24. It was then decided to open the cavity permanently since the patient's course was definitely downhill. The operative note follows: "This

man has had a large cavity at the right upper lobe. It is a tension cavity with pressures of +12, +20. Rubber tube proved very irritating. Therefore, it was decided to open the cavity. Under satisfactory local anaesthesia a U-shaped incision was made in the axilla and a flap freed down to the muscular layer. This was elevated, bleeding points clamped and tied, and with the cautery knife an incision was carried down to the fourth rib. The periosteum was then destroyed with the cautery and the rib removed. Through the rib bed, pus was aspirated from the cavity. The incision was then carried down into the cavity, using the actual cautery to open the cavity for a distance of about one and one-half inches. The skin flap was then fixed to the upper layer of the cavity wall with two nonabsorbable mattress sutures. The skin flap fell in nicely and its margins were sewed with three stitches through the muscular layer. The lower portion of the wound was closed with chromic gut. The cavity was loosely packed with iodoform gauze and vaseline-gauze laid over the edges of the skin wound." For two days following the operation the patient's temperature rose to 105.5°F. Thinking this might be due to the iodoform packing, the pack was removed and plain gauze substituted. The patient's temperature at once fell to normal for the first time in many months. Convalescence was uneventful. The wound was packed with gauze until no cavity remained, only a dimple in the skin showing where the cavity had been. The lung beneath the thoracoplasty reëxpanded and the patient was discharged from the sanatorium with a negative sputum and no wound drainage. He began working as a dentist September 25, 1940, and has been well and at work ever since. This patient was later shown to be sensitive to iodine. Although packed with iodoform gauze, none of the other patients so treated have had the sharp temperature rise shown by this patient.

The axillary approach was chosen in this case because the cavity was large and easily accessible from the axilla. In other cases it was necessary to approach the cavity from behind.

Case 2: A single, white female, age nineteen, was seen November 22, 1938, with a large spherical apical cavity on the left side. She was sent to the Tuberculosis Division of the Ross General Hospital and a left pneumothorax begun at once. This proved unsuccessful, the cavity being firmly adherent to the chest wall above and posteriorly. The lung was allowed to expand and the cavity needled, a +2, +12 reading being obtained. It was then decided to do an extrapleural pneumothorax, which was done February 3, 1939. The lung was freed over the apex but in carrying the dissection downward the free pleural cavity was entered, producing a combined intra- and extrapleural pneumothorax. Subsequently the cavity, although changed in position, did not change in shape or size and this procedure was also abandoned. After expansion it was found that the intracavitary pressures varied from +12 to

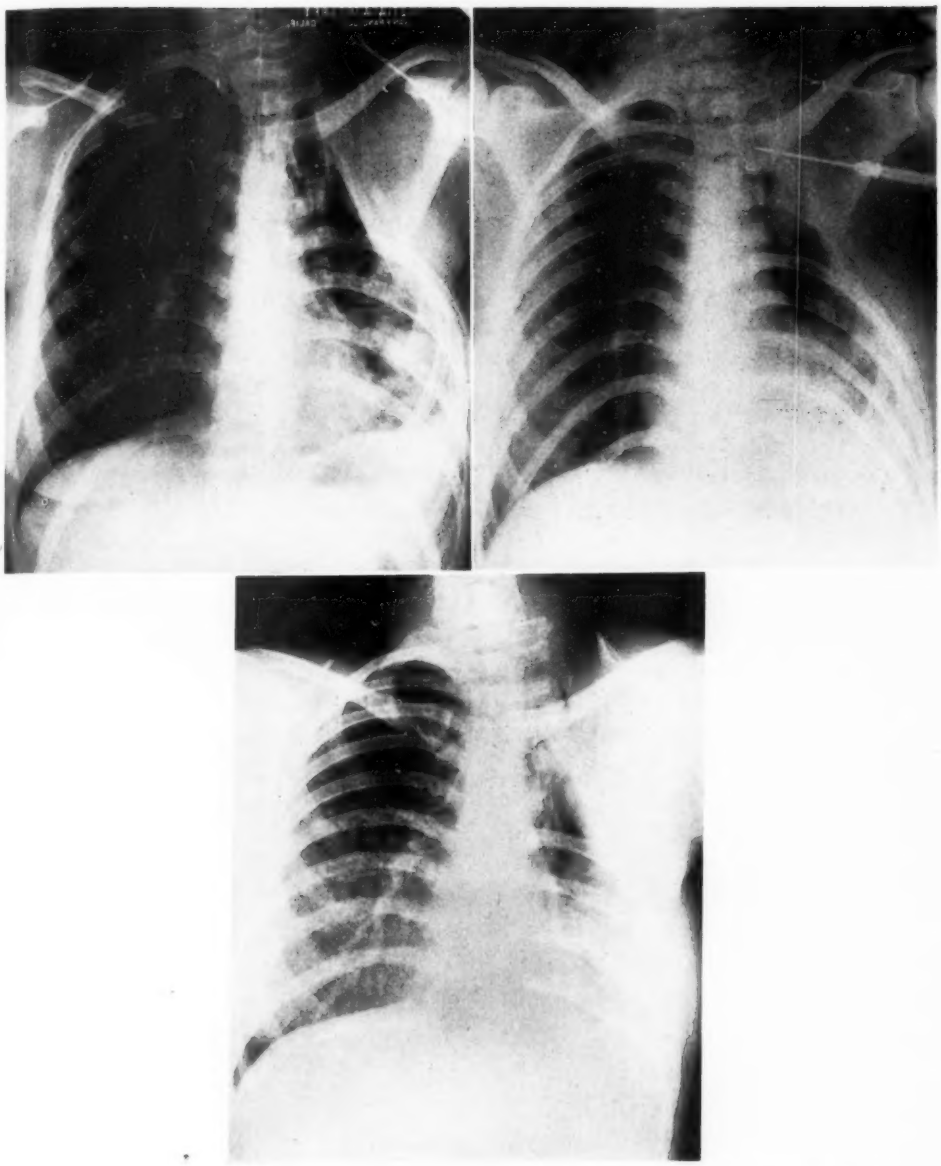

FIG. 1. (Top left.) Case 2. April 22, 1940. Residual cavity beneath left thoracoplasty. It is plainly seen as an oval shadow extending well above and below the clavicle.

FIG. 2. (Top right.) Case 2. August 27, 1940. A needle has been inserted into the cavity and left exposed to atmospheric pressure. No cavity can now be seen.

FIG. 3. (Bottom.) Case 2. January 6, 1941. A skin flap has been inserted into the cavity, using the posterior approach. The cavity disappears at once.

neutral. Choosing a period of neutral pressure a first-stage thoracoplasty was done on October 27, 1939. The cavity diminished in size but later "blew up" again. A second stage was done, taking sections of the fourth, fifth and sixth ribs and a portion of the scapula on January 18, 1940. Following this, the cavity became much smaller, but remained as a slit near the spine and needling showed a rather consistently high pressure. It was therefore decided to open and decompress the cavity, which was done through the posterior approach on September 27, 1940. The operative note follows: "This young woman has had a tension cavity in the left upper lobe. Originally it was a balloon cavity with a high pressure. It diminished rapidly when a needle was left in the cavity and thoracoplasty was done when the pressure seemed to be neutral. Following the thoracoplasty the cavity blew up again, however, and was found to have very high pressure. It was decided that the only way to attack this cavity beneath the thoracoplasty was by open drainage. Accordingly an elliptical incision was made crossing the old scar and extending almost to the midline, beginning and ending at the border of the scapula. The flap formed in this manner was dissected free and elevated. The incision was then carried down through the trapezius muscle and a needle was inserted into the cavity. With the cautery the incision was carried further. Two needles were then placed in the cavity one above the other and with the cautery an incision was made between them until the cavity was reached. The incision was then carried upward and downward until about three inches of pleura was incised and the posterior wall of the cavity unroofed. The flap was then fastened to the pleura with two silk sutures and the cavity was packed with gauze. Before packing a very tiny bronchus could be seen bubbling on the anterolateral wall when the patient strained or coughed." Figures 1, 2 and 3.

The patient had a very smooth postoperative course. After the first month the sputum and wound drainage were negative for tubercle bacilli, and the patient was given exercise. She was discharged from the hospital November 25, 1940.

Our present series comprises 7 cases. The axillary approach was satisfactory in 2. The posterior or paravertebral approach was used in 5. Sputum conversion has taken place in the first 5 cases so treated. One of the 5 required secondary bronchial closure. The remaining 2 have been of such recent date (two and three months respectively) that sputum conversion cannot be considered certain.

SUMMARY

An operative procedure, designed to overcome both the extrinsic and intrinsic factors of persistent cavitation beneath thoracoplasty, has been described. In no instance has any untoward complication been encoun-

tered. Sputum conversion and cavity closure have been obtained in 5 out of 7 cases reported. In the 2 unsuccessful cases, time has been insufficient to allow conclusions to be drawn, but their clinical course to date would indicate a probable outcome similar to the 5 cases with closed cavities. If future results continue to be as good as those in the past, it would seem that a very conservative type of thoracoplasty is justified, with the knowledge that if an unclosed tension cavity persists a flap operation can be done without subjecting the patient to a drastic revision.

SUMARIO

El procedimiento operatorio aquí descrito propónese eliminar los factores tanto extrínsecos como intrínsecos que hacen persistir las cavernas debajo de la toracoplastia. En ningún caso se observó complicación alguna contraproducente. En 5 de 7 casos comunicados se obtuvo la transformación del esputo y el cierre de las cavernas. En los dos fracasos aparentes el tiempo transcurrido no permite todavía sacar conclusiones, pero la evolución cliínica hasta la fecha indica que el desenlace será probablemente semejante al de los 5 casos en que se cerraron las cavernas. Si los resultados continúan siendo tan buenos en el futuro como hasta ahora, parece que está justificada una toracoplastia muy conservadora, con el conocimiento de que si persiste sin cerrarse una caverna de tensión, puede realizarse una operación de colgajo sin someter al enfermo a una nueva intervención drástica.

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VITAMIN C TREATMENT OF MUCOUS MEMBRANE TUBERCULOSIS[1,2]

EMIL BOGEN, LAWRENCE HAWKINS AND EDWIN S. BENNETT

A specific effect of vitamin-C deficiency on the production of ulcerative intestinal tuberculosis in guinea pigs was reported by McConkey and Smith (1) who found that, although all guinea pigs fed adequate amounts of tuberculous sputum developed generalized tuberculosis, only those with coincident vitamin-C deficiency revealed tuberculous intestinal ulcerations. This experimental observation of the development of ulcerative tuberculous lesions of the intestine in guinea pigs suffering from vitamin-C deficiency was confirmed at the Olive View Sanatorium (2), and more recently by Greene and coworkers (3). A similar mechanism in the development of intestinal tuberculosis in humans was suggested by McConkey (4), who recommended the prophylactic and therapeutic administration of codliver oil in tomato juice for such patients. The Raybrook workers reported successful experience with this therapy which has been widely used in other places (5), despite a few discouraging results (6).

The possibility that vitamin C might be of importance in the pathogenesis of ulcerative lesions of mucous membranes, other than those of the intestine, was suggested by the frequent coincidence of laryngeal and intestinal tuberculosis in the same patient, as well as by the clinical improvement in laryngeal symptoms in a small group of patients given vitamin C here several years ago. The increased attention attracted to tracheobronchial tuberculous lesions in recent years and the poor prognosis of such lesions (7) suggested the possibility that vitamin-C therapy might be useful in this condition. Accordingly, 15 patients suffering from tuberculous tracheobronchitis were given additional vitamin C for a period of three months. Although the general condition of pulmonary tuberculosis in these patients showed little difference as a result of treatment, there appeared to be a beneficial effect on the visible lesions in the

[1] From Olive View Sanatorium, Olive View, California.

[2] With the aid of Work Projects Administration, Project No. 665-07-3-223, Los Angeles County, California.

respiratory passages (8). This experiment was too small to justify definite conclusions, but seemed sufficiently promising to warrant further and more extensive clinical experimentation.

Nearly 200 patients at the Olive View Sanatorium were selected for this investigation, because of some ulcerative or mucous membrane lesions revealed by means of bronchoscopic, laryngoscopic, proctoscopic or radiological examinations. Names of these patients were tabulated, according to the extent and severity of the lesions. They were then divided into equivalent groups by assigning each consecutive name in rotation to a different group. Most of the patients were receiving the regular sanatorium diet during all this time, whose menus have been calculated by the dietitian to provide adequate intake of calories, protein, carbohydrates, fat, minerals and vitamins, as taught in standard dietetic texts. Vitamin-C intake so supplied, however, averaging in the neighborhood of 75 mg. per day, is apparently inadequate for patients with tuberculosis, as shown by blood vitamin levels and urinary saturation tests.

The patients in the first group (A) received a dietary supplement of two heaping teaspoonfuls of a fortified chocolate malted milk powder ("Cal-C-Tose" (9)) in a glass of milk three times daily. This contained substantial increments of practically all of the dietary factors, including 150 mg. of vitamin C.

The patients in the second group (B) similarly received two heaping teaspoonfuls three times daily in milk of the regular malted milk powder dispensed at this Sanatorium. This treatment resembled that of the first group in calories and general chemical composition, but was lacking in the additional calcium and vitamins present in that material.

Patients in the third group (C) were given two vitamin tablets (9), each containing 25 mg. of synthetic crystalline cevitamic acid in lactose three times daily, making a total of 150 mg.

The patients in the fourth group (D) each received two calcium tablets, each containing 5 grains or 300 mg. of calcium lactate three times daily, making a total of about two grams of calcium lactate per patient per day. This was considered practically as a placebo, although calcium has been advised in the treatment of intestinal tuberculosis (10).

Patients in the fifth group (E) each received two heaping teaspoonfuls of a seaweed preparation ("Nutramin" (11)) containing minerals and vitamins, but with the express omission of added vitamin C. Previous experiments with this material had indicated that it improved the nutri-

tion of guinea pigs otherwise on our standard diet and suggested perhaps a slight retardation in the tuberculous lesions in these animals.

Patients in the sixth group (F) were given eight ounces, twice daily, of a fruit-vegetable drink, containing orange, tomato and pineapple juice together with alfalfa, carrots and other vegetables.

Patients in the seventh group (G) were not given any special medication, but were kept as a sort of psychological control in whom laboratory and other observations were made but no special treatment given, thus checking on the mental stimulation which so often results in apparent improvement in patients taking any new treatment.

Since many of the treatments had some features in common, it is convenient for purpose of comparison with larger figures to group together the series having such common features in considering their initial status and the results of treatment. Thus, groups A, C and F were all given increased amounts of vitamin C, averaging 150 mg. per day, in excess of their regular diet. Groups B, D and E were given increased calcium and other materials without vitamin C, while group G received no special treatments and thus lacked the psychic as well as the intrinsic value of the treatments.

The age and sex distribution of the patients in this study was similar to that generally encountered at the Olive View Sanatorium and similar institutions, averaging around thirty years, but ranging from less than ten to more than fifty years of age, with an excess of females. The distribution by age and sex in the different series with or without vitamin C, or without any treatment, was quite similar and, in fact, each of the special groups treated showed a similar age distribution.

The disease was generally quite extensive in these patients, nearly 80 per cent being in the far-advanced stage and the remainder moderately advanced. No minimal or childhood type patients, in whom a good prognosis is the rule, were included. It is not believed, therefore, that differences in age, sex or stage could have affected the findings in this study.

More than 90 per cent of the patients in this study had tuberculous lesions of the mucous membranes in an accessible or demonstrable site. Thus, 96 showed tuberculous tracheobronchitis demonstrable by bronchoscope; 46 had laryngeal tuberculous lesions visible with the laryngoscope; 68 had clinical or radiological evidence of intestinal tuberculosis, and 27 had anorectal lesions due to tuberculosis.

Tuberculous tracheobronchitis was observed in nearly half of these patients through the bronchoscope, the lesions consisting of granulations

with only slight ulceration in 36 instances, and of more extensive ulceration in 38, while only 22 manifested at the outset the late stage of fibrosis with contraction or stenosis. The distribution of these 3 types of lesions was also essentially similar in the different groups treated, those receiving the vitamin C having a slight excess of patients with extensive tracheo-

TABLE 1

Initial condition

	TREATMENT CONTAINING VITAMIN C (ACF)	OTHER DIETARY SUPPLEMENTS (BDE)	NO DIETARY SUPPLEMENT (G)	TOTAL
Total	82	77	37	196
Sex:				
Male	29	31	7	67
Female	53	46	30	129
Age:				
−25	30	25	12	67
25–34	27	31	14	72
35 +	25	21	11	57
Stage:				
Moderately advanced	15	20	7	42
Far advanced	67	57	30	154
Tuberculous Tracheobronchitis	45	37	14	96
Slight ulceration	17	14	5	36
Extensive ulceration	18	13	7	38
Stenosis	10	10	2	22
Tuberculous Laryngitis	23	20	3	46
Slight	17	12	3	32
Moderate	3	6	0	9
Extensive	3	2	0	5
Tuberculous Enteritis	32	31	5	68
Anorectal Tuberculosis	11	14	2	27

bronchial ulceration, while the entirely untreated group showed less ulceration.

The dietary supplements provided by these various treatments were by no means the only therapeutic measures administered to these patients. Nearly 90 per cent of them were receiving some form of collapse therapy consisting of pneumothorax or phrenic paralysis or the combined proce-

dure; 10 per cent of them had received thoracoplasty and almost an equal number, extrapleural pneumothorax. One had received a lobectomy, while another had been treated with the newly suggested procedure of prolonged cavity aspiration devised by Monaldi.

The results of treatment, so far, may be considered either with reference to the general state of the patient or the pulmonary lesion, or with regard to the various complications for which this group was selected. The status at the time of discharge, recorded according to the classification of the National Tuberculosis Association, may give some indications of the

TABLE 2

General results

	TREATMENT CONTAINING VITAMIN C (ACF)	OTHER DIETARY SUPPLEMENTS (BDE)	NO DIETARY SUPPLEMENT (G)	TOTAL
Total	82	77	37	196
Discharge Condition:				
Arrested	10	4	3	17
Quiescent	10	19	3	32
Improved	20	16	8	44
Unimproved	10	3	5	18
Dead	10	8	3	21
Still in Olive View	22	27	15	64
Weight Change:				
Gain	36	33	10	79
Same	4	4	5	13
Lost	22	21	9	52
Unknown	20	19	13	52
Clinical Impression:				
Improved	48	37	9	94
Same	23	23	16	62
Worse	11	17	12	40

effects of the treatment on the pulmonary lesion. The number of deaths so far, two years from the inception of the experiment, 19 among 196 patients, represents about 10 per cent of the total number observed. The slight differences in mortality rates observed in the different groups may be ascribed to mere chance variation occurring among such small numbers. The condition on discharge of those discharged living, similarly shows little significant variation. Subjectively, both patients and physicians felt that the general condition of the patients receiving vitamin C

was better than that of those patients receiving other treatments or receiving no treatment at all, although the status of the lung conditions, as shown by discharge diagnosis, did not support this impression. Perhaps the opinion of physician and patient may have been affected by the course of the complications in many cases, more than by the course of the pulmonary lesion itself.

Another simple indication of the response of the patient to treatment may be sought in the change in weight during the course of this treatment. The regular monthly weighing of patients in the wards was omitted in 52 instances, because the patient was confined to bed. Among the others, 79 showed a gain in weight, 52 a loss in weight and 13 remained stationary. Little difference can be observed in the weight curves of those receiving the different treatments. The changes in laboratory findings during the course of this experiment also show relatively little difference between the various groups examined.

Determinations of the vitamin content of the twenty-four-hour urine specimens by the Tillman indophenol reagent averaged less than 5 mg. per patient at the beginning. In all groups there was some increase in this vitamin excretion with the advance of the summer, but in the patients not given extra vitamin C this increase was slight, averaging little over 5 mg., and exceeding 10 mg. per day only in exceptional instances. In the patients receiving vitamin C in addition to their regular diet, the increase was much greater, though still below what would have been expected in normal persons, averaging about 30 mg. per day.

Despite the absence of significant differences disclosed by the previous observations and the general condition of the patients at discharge or as shown by their laboratory findings, marked changes were observed in the specific ulcerative lesions of the respiratory and alimentary tracts studied in this series. Bronchoscopic examination, as well as clinical observation, revealed improvement in nearly 90 per cent of the patients receiving additional vitamin C, as compared to less than half of those receiving the control treatments, or not receiving any special therapy. A similar beneficial effect was observed in the case of tuberculosis of the larynx, three-fourths of those receiving the vitamin showing improvement, as compared to only half of those not receiving this treatment.

Repeated X-ray observations or other more reliable evidences of change in the gastrointestinal tuberculosis cases are not available, but the clinical symptoms in these patients were reported as markedly ameliorated in the majority of instances in which any such report could be obtained, while

the majority of those patients not receiving the vitamin-C treatment report definite aggravation of their gastrointestinal symptoms. The rectal lesions accessible to direct and proctoscopic examinations showed improvement in two-thirds of the cases receiving vitamin C, as compared to only half of those not receiving this vitamin, but the numbers here are too small to be significant.

No differences in the general treatment of these patients were intentionally inaugurated as a result of the various treatments given, but a re-

TABLE 3

Changes in mucous membrane lesions

	TREATMENT CONTAINING VITAMIN C (ACF)	OTHER DIETARY SUPPLEMENTS (BDE)	NO DIETARY SUPPLEMENT (G)	TOTAL
Tuberculous Tracheobronchitis	45	37	14	96
Improved	23	11	2	36
Same	19	17	9	45
Worse	3	9	3	15
Tuberculous Laryngitis	23	20	3	46
Improved	19	11		30
Same	2	1	1	4
Worse	2	8	2	12
Tuberculous Enteritis	32	31	5	68
Improved	8	1	0	9
Same	1	2	1	4
Worse	3	6	2	11
Unknown	20	22	2	44
Anorectal Tuberculosis	11	14	2	27
Improved	3	3	0	6
Same	0	1	0	1
Worse	2	1	1	4
Unknown	6	9	1	16

view of the different measures actually applied suggests that those receiving vitamin C did have somewhat more agressive local treatment of the tracheobronchial lesions. This may have been partly a result of the spontaneous improvement which these lesions were showing, as advancing lesions are less apt to receive active treatment.

Other agents might possibly have been found effective if the regular diet in the Sanatorium had not been already adequate with regard to them. Additional vitamin C would probably have produced no such

good results if the patients had already received a surplus of this vitamin in their diet. Patients with tuberculosis require a greater intake of this vitamin than do healthy individuals (12). Vitamin C is readily destroyed in the course of culinary preparations and little stored in the body. A deficiency in this vitamin, similar to that observed in this group, may therefore be expected in other patients suffering from similar complaints. Complications of ulcerative tuberculosis of mucous membranes might perhaps be diminished or prevented in man, as in the guinea pig, by the administration of surplus vitamin C. Their occurrence may, therefore, be *prima facie* evidence of a subclinical scorbutic condition.

SUMMARY

The effect of various dietary supplements on the course of pulmonary tuberculosis and ulcerations of mucous membranes in this disease has been investigated in nearly 200 patients at the Olive View Sanatorium. No marked effect on the course of the pulmonary disease could be shown for any of the various dietary supplements administered. Subjectively, more improvement was reported in the patients receiving vitamins than in those not receiving these factors. The ulcerated mucous membrane lesions in the tracheobronchi, larynx, intestine or rectum visibly improved following the administration of vitamin C. This finding is consistent with observations previously made here in a smaller series of patients, and is consistent with the results of animal investigations both here and elsewhere. Vitamin C is by no means a cure for tuberculosis. Vitamin-C deficiency, however, appears to increase the incidence of certain serious complications in this disease. Its abundant administration, therefore, may be recommended for the purpose of preventing or treating these complications.

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THE EFFECT OF ARSPHENAMINE ON TUBERCULOSIS IN SYPHILITIC ANIMALS[1, 2]

WALSH McDERMOTT, BRUCE WEBSTER AND DONALD MACRAE

Ever since the introduction of arsphenamine there has been controversy among clinicians and investigators as to its effect upon tuberculous lesions occurring in the syphilitic patient.

The problem of the effect of the two diseases upon each other has been investigated both from autopsy statistics by Landsberger (1) and experimentally by Ohnawa (2) and by Aronson and Meranze (3, 4). Landsberger estimated the incidence of syphilis from the postmortem protocols of 5,323 patients, 1,267 of whom had florid tuberculosis, and concluded that no effect of tuberculosis upon the incidence of syphilis could be demonstrated. Aronson and Meranze (3, 4) showed that the syphilitic rabbit's response to a tuberculous infection was histologically altered as compared with the nonsyphilitic animal and that syphilitic animals presumably cured by arsphenamine therapy still showed this altered tissue response to the introduction of tubercle bacilli. Ohnawa (2) injected tubercle bacilli into one testicle and *Treponema pallida* into the other testicle of rabbits. Both testicles were injected simultaneously in one group, while in another there was an interval between the infection with tuberculosis and the inoculation with syphilis. When syphilis was given after tuberculosis was established, the syphilitic changes were less marked and healed more quickly than in the simultaneous double infections. This was interpreted as showing that, through the preceding tuberculous infection, a certain general resistance against subsequent syphilitic infection is attained. Tuberculosis spread to the opposite testicle in both groups, but in the group with the recently healed syphilis, tuberculosis spread more slowly and was milder than in simultaneous double infection in which the syphilis had been healed for some time. This phenomenon indicated that after the resorption of

[1] From the Syphilis Clinic of the Department of Medicine, New York Hospital and Cornell University Medical College, New York, New York.

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syphilitic lesions there remained a definite, although transient, "tissue immunity." However, despite the presence of this transient immunity, the author found that the infection of the tuberculous animals with syphilis had an unfavorable influence on the course of the tuberculosis when compared with control animals.

Reports on the effect of arsphenamine on coexistent tuberculosis and syphilis have been largely clinical, many dating back to the time when the X-ray was not generally used and when only a few injections of arsphenamine constituted the complete treatment of syphilis. In this voluminous literature many contradictory opinions are expressed and only the more recent reports contain the data now considered essential to a proper consideration of the two diseases. Part of the difficulty lies in the fact that in general the two diseases are seldom treated by the same group of physicians and that the specialist in the treatment of the one disease has little experience in the evaluation and handling of the other. The extreme variability in the course of either disease in the patient, the long period of time during which either disease may remain potentially active, and the difficulty of evaluating the amount of rest obtained by ambulatory tuberculous patients, are some of the many factors which make the collection of a clinical series well nigh impossible.

Moore and Padget (5), in a review of this subject, summarize some of the recent series, point out their inadequacies as a basis for a critical evaluation, supply some clinical data of their own which they admit are similarly inconclusive, and express the opinion that because of these many variables the decision cannot be reached by clinical study alone but should be investigated by animal experimentation.

There are very few data on the effect of the arsphenamines on experimental tuberculosis. Renon and DeLille (6) used atoxyl in the treatment of tuberculosis in humans and guinea pigs and found that it had neither a beneficial nor a deleterious effect. Details of experiments are not given. Arkin and Corper (7) in 1916 found that neoarsphenamine in dilutions of from 1 per cent to .001 per cent had no germicidal action on human tubercle bacilli *in vitro* in twenty-four hours at 37°C. and that, when injected parenterally into a tuberculous guinea pig, did not accumulate in the tuberculous tissue. Smith (8) in 1922 found that neoarsphenamine and silver arsphenamine had a very slight inhibiting action on the growth of tubercle bacilli *in vitro* but had none on their pathogenicity. When it was administered to tuberculous guinea pigs no favorable influence on the course of the disease was shown.

EXPERIMENTAL

The following experiments were undertaken to observe the effect of arsphenamine upon tuberculosis in syphilitic animals. The rabbit was the animal chosen because it is susceptible to both syphilis and tuberculosis and has readily accessible veins for repeated arsphenamine treatment.

Preliminary attempt: In an effort to simulate the conditions of human adult-type tuberculosis as much as possible, our first attempts were made with rabbits sensitized to Old Tuberculin by inoculation with avirulent human tubercle bacilli (R1 Saranac Laboratory strain) and reinoculated intratracheally with virulent human bacilli (H37 Saranac Laboratory strain, dosage 3 mg. wet weight). This resulted in complete failure as the resulting tuberculosis was so variable in its extent and course that no interpretations of the effect of the syphilitic infection and arsphenamine therapy were possible. Of 53 animals followed over a five-month period, 21 died of advanced pulmonary tuberculosis, 12 were obviously dying when sacrificed and 20 were recovering. The incidence of deaths was steady from beginning to end with no increases after the introduction of syphilis or arsphenamine. Because of this experience it was felt that a different type of tuberculosis would be necessary to permit the carrying out of the experiments.

Materials and methods: A twenty-two-day growth of a bovine type of tubercle bacilli (B1 Saranac Laboratory) grown on Proskauer and Becks liquid medium was dried between sheets of filter paper and weighed. The dried culture was ground by rotating it with ball bearings in a Florence flask into which saline was slowly added. The resulting suspension contained 0.5 mg. per cc. X-ray films of the rabbits' chests were then taken by the method of Greenberg (9). Blood Wassermann reactions were performed as follows: The serum to be tested was inactivated at 60°C. for thirty minutes. Three-tenths of a cc. of this serum was placed in two tubes (one for control), 0.1 cc. antigen (an ether insoluble, acetone insoluble, alcoholic extract of beef heart cholesterinized to 1 per cent) was introduced into one tube and two and one-half units of complement into both tubes. The tubes were kept in the ice-box for four hours; 0 2 cc. sensitized sheep cells were added, the mixture was incubated for fifteen minutes at 37°C., and the test read.

Fifty rabbits, which had previously had chest X-ray films and blood Wassermanns, were inoculated intravenously with 0.5 cc. of a suspension containing 0.25 mg. of tubercle bacilli. Two weeks later they all

gave positive reactions to the intracutaneous injection of Old Tuberculin (50 mg.). Blood Wassermanns were repeated and 32 of the animals were inoculated in the right testicle with 1.0 cc. of a testicular suspension containing approximately three *Treponema pallida* per oil immersion field (Nichols strain). Three weeks after inoculation with syphilis or six weeks after inoculation with tubercle bacilli, the animals were divided into three groups.

Groups I and II were composed of animals with both tuberculosis and syphilis; group III of animals with tuberculosis alone. The presence of syphilis in the animals to be treated was established at this time by the demonstration by darkfield examination of *Treponema pallida* in material obtained by testicular puncture. All animals inoculated with syphilis were so proven to be positive with the exception of one in the control group from which a testicular transfer to a normal rabbit at the termination of the experiment was made. This has been negative thus far. X-ray films of the chest were taken on all animals. Treatment with arsphenamine of the animals in groups I and III was begun. Old arsphenamine, previously neutralized and diluted so that 1.0 cc. contained .01 g. of the drug was given in doses of 10 mg./kg. at weekly intervals for ten weeks. The dosage of arsphenamine was chosen on the following basis. In the treatment of syphilis in humans, the usual single dose of arsphenamine is 0.4 g. for a 60 kg. man or approximately 7 mg./kg. Twenty or 30 such injections are given to patients over a period of eighteen to twenty-four months. The minimal curative dose of arsphenamine in rabbit syphilis, given in one injection, is 12 mg./kg. (10). Therefore, 10 mg./kg. for ten weeks represents moderately intensive arsenical therapy.

Chest X-ray films were taken one week after the last injection of arsphenamine. At the same time blood for the Wassermann reaction was obtained. Three weeks later the animals were sacrificed. Lungs, liver, spleen, kidneys and testes were preserved in 5 per cent formalin. Estimation of the amount of tuberculosis present was made according to an arbitrary classification.

The duration of the experiment was twenty-six weeks. During this period the animals were examined at weekly intervals. The course of the syphilis and of the tuberculosis was followed by the examinations detailed above.

Deaths during the course of the experiment: Six animals died two to five weeks after inoculation with tuberculosis but before arsphenamine

was given. In only 3 of these could the cause of death possibly have been tuberculosis, the others dying of broken backs or diarrhoea. Autopsies were performed on 5 of the 6 animals and showed, in every case, normal crepitant lungs which were studded with tiny tubercles averaging 0.5 mm. in diameter. No pneumonic areas were present. Of the 44 animals in the three groups, there were only 2 deaths after arsphenamine was started, at two and five weeks respectively. In one, multiple chronic skin abscesses were a debilitating factor and in the other no definite cause of death could be demonstrated but there was not enough anatomical evidence of disease at autopsy to attribute the death to tuberculosis. One of these animals was from an arsphenamine-treated group, the other from a control group. Only 2 of the 44 treated animals failed to gain weight, one being the animal with multiple abscesses noted above.

Clinical lesions of syphilis: Eleven of the 13 animals in group II (no arsphenamine) developed clinical lesions of syphilis consisting of nodular orchitis, usually bilateral and accompanied by chancres. In 3 of the group I animals (arsphenamine treated) small testicular nodules which disappeared promptly were felt early in the course of therapy. No interstitial keratitis or bone lesions were observed in any of the animals.

Wassermann reactions: Because the effect of tuberculosis upon the blood Wassermann reaction is disputed and has recently been the subject of an extensive clinical investigation (11), data on the behavior of this reaction in the first series of 54 rabbits with human type tuberculosis are included here as well. The specificity of the Wassermann reaction in syphilis in the rabbit is denied by many investigators because of the occurrence of biological false positives. However, Eagle (12) has shown that a part of the discrepancy between various reports is due to the variety of techniques used, and there are workers (Kemp and Chesney (13)) who believe that the procedure is of value if a technique of the proper sensitivity is selected.

Sera from 54 tuberculous rabbits which had not been infected with syphilis were tested by the technique described above. Fifty-two tests were negative, one was ++, and one was anticomplementary. Seventeen of these animals were retested a month later and were all Wassermann-negative. These same 17 were then given weekly injections of arsphenamine, 10 mg./kg. for a period of ten weeks with routine Wassermanns every four weeks. These were uniformly negative. Another 17 of the original 54 Wassermann-negative tuberculous animals were

infected with syphilis after tuberculosis was well established. Four weeks after the infection with syphilis, 2 had positive Wassermanns (++++), one was doubtful (+), and 14 were negative. At eight weeks, 11 were positive (++++), and one was anticomplementary (12 survivors), while at fourteen weeks after infection 4 were positive (++++), 3 were doubtful (+ to +++) and 4 were negative. The remaining 16 of the original 54 Wassermann-negative tuberculous animals were inoculated with syphilis and treated with arsphenamine as soon as aspiration of testicular fluid was positive for treponemes but before any clinical lesions had developed. Four weeks after infection 6 were positive and 7 negative, at eight weeks 7 were negative, one positive, one doubtful and one anticomplementary (all positive at four weeks) and fourteen weeks after infection, after ten arsphenamine treatments (8 survivors), all 8 were negative including the positive and anticomplementary reactors at four weeks.

In untreated syphilitic rabbits the Wassermann test with this technique was surprisingly sensitive but represented a relatively fleeting phenomenon, being present in the majority of instances (11 of 12) only at eight weeks after the inoculation with syphilis. As this is a period when the testicular lesions are usually quite evident, it is of little diagnostic help. Its development at eight weeks was prevented in 9 of 10 animals by arsphenamine therapy. Tuberculous infection alone had little effect on the specificity of the test as there was only one instance of a doubtful positive (++) in the sera of 54 tuberculous animals.

In the experiment in which the bovine tubercle bacillus was used, the tests were performed immediately preceding inoculation with tuberculosis, again just before the infection with syphilis; eight weeks later and at the conclusion of the experiment (sixteen weeks after inoculation with syphilis).

Sera from 50 animals were all Wassermann-negative before inoculation with tuberculosis and were all negative eighteen days afterward, at a time when all the animals were tuberculin-positive. Twenty-seven of these animals were infected with syphilis, 14 receiving arsphenamine as soon as the diagnosis of syphilis was established. Eight weeks after infection with syphilis all 14 of the treated animals and all 15 of the tuberculous nonsyphilitic animals were Wassermann-negative, while of the 13 untreated syphilitic animals there were 4 positives (++++), one doubtful positive (+++) and 8 negatives. Three of these 8 negative reactors showed positive (one) or doubtful (two) reactions at six-

teen weeks, making a total of 5 positive and 3 doubtful reactions occurring in 8 of the 13 animals at some time during the course of the infection. The remainder of the sera tested at sixteen weeks showed 5 anticomplementary and 20 negative reactions.

Combining the data, of 104 tuberculous rabbits whose sera were tested by this Wassermann technique, all were negative save for one doubtful (++) reaction. Not one of the 25 animals of this number which was not subsequently infected with syphilis developed a positive reaction over a period of fourteen weeks, although 5 gave anticomplementary results at sixteen weeks. Although the test was equally specific in both experiments, it was much less sensitive in the second (5 of 13 positive), possibly due to the fact that the latter experiment was conducted during the hot summer months when rabbit syphilis tends to run a more benign course.

TABLE 1

Results of Wassermann reactions

	NUMBER	POSITIVE	DOUBTFUL	NEGATIVE	ANTICOMPLEMENTARY
Tuberculous nonsyphilitic	104	0	1	103	0
14 weeks later	25	0	0	20	5
Tuberculous syphilitic untreated					
8 weeks after syphilitic infection	25	15	1	8	1
14–16 weeks after syphilitic infection	20	5	5	10	0

Chest X-rays: X-rays of the chest were taken before inoculation with tuberculosis and at six weeks and sixteen weeks thereafter. The latter two dates were just before and just after the ten weeks of arsphenamine treatment. Thirty-two of the 44 animals X-rayed at six weeks showed definite, diffuse, miliary type mottling throughout both lung fields. Eight animals showed shadows which were considered to be questionable, although probably positive, and 4 were definitely negative.

The extent of involvement as judged by the X-ray films interpreted as positive was uniform throughout.

Too much significance should not be placed on negative or questionable X-ray findings in rabbit tuberculosis as it has been our experience and that of other observers (14) that, because of the size and position of the heart and other factors, there can be a considerable amount of tuberculosis demonstrable at autopsy which was not evident at all in X-ray films.

X-ray plates taken at sixteen weeks (one week after the end of the arsphenamine treatments) showed complete disappearance of the previously demonstrated shadows in all but 3 animals (2 from group II and one from group III), and in these 3 there was marked and almost total clearing.

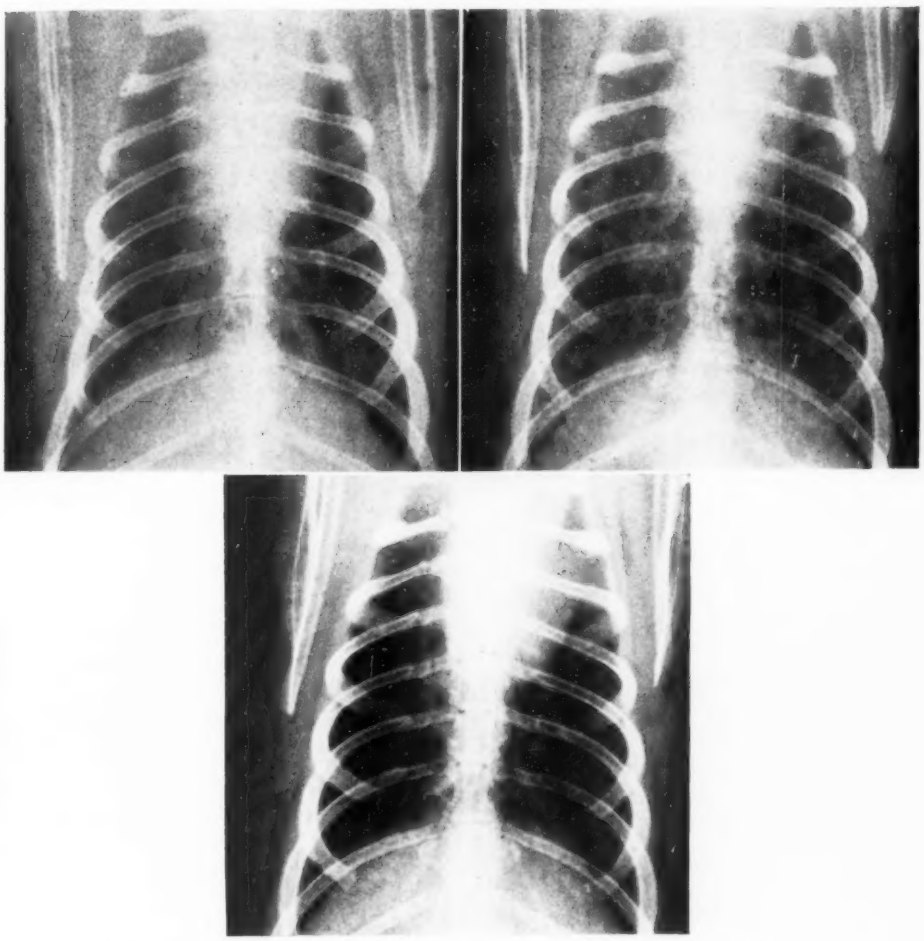

FIG. 1. Chest X-ray films of a rabbit showing the course of tuberculosis
(left) Normal chest X-ray film before inoculation with tuberculosis.
(right) Chest X-ray film taken six weeks after inoculation with tuberculosis showing uniform, fine, bilateral mottling.
(center) Chest X-ray film taken sixteen weeks after inoculation with tuberculosis showing the complete disappearance of the shadows present at six weeks.

Pathological findings: All 44 animals were found to have grossly demonstrable pulmonary tuberculosis.

Upon opening the chest cavities, all the lungs were normal in size and free from adhesions to the chest wall or diaphragms and the uninvolved portions were pink and glistening. The individual lesions were similar throughout the entire series, varying mainly in distribution, consisting of slightly raised, yellow-white, smooth, firm areas ranging from 0.5 to 2 mm. in diameter. These were surrounded by apparently normal lung tissue and on section showed a uniform white caseous appearance. In some of the lungs, greenish brown areas of the same diameter as the other lesions were present. These contained tiny emphysematous blebs. In a few instances larger (1 to 2 cm.), though similar, lesions were present. On section these showed a white cheesy

TABLE 2

X-ray findings at six and sixteen weeks after inoculation with tuberculosis

	6 WEEKS	16 WEEKS
Group I (Tuberculosis, syphilis and arsphenamine)	9 positive 3 questionable 3 negative	all negative
Group II (Tuberculosis and syphilis)	11 positive 2 questionable 1 negative	all but 2 negative and those show marked clearing
Group III (Tuberculosis and arsphenamine)	12 positive 3 questionable	all but 1 negative; that showed marked clearing

material encapsulated in a thin wall which in some cases had partially excavated, leaving cavities the largest of which was 1 cm. in diameter. No areas of consolidation were present.

Comparative estimation of pulmonary tuberculosis: An attempt was made to estimate the extent of involvement of the lungs from gross examination. The amount of tuberculosis present varied and no such quantitation would be accurate when applied rigidly. However, certain patterns occurred with sufficient uniformity to permit division of the material into two grades with a reasonably clear-cut endpoint. In many there were only a few isolated areas scattered over the lung surface. In about one-half, however, there was a uniform seeding of the entire substance of both lungs with these 1 to 2 mm. tubercles. Division into two grades was made on the basis of the uniformity of the distribution of these tubercles throughout both lungs.

Grade I: Isolated 1 to 2 mm. white tubercles occurring rarely (one to three per animal) or scattered discretely in irregular arrangement in several lobes.
Grade II: Uniform, diffuse studding of all lobes with 1 to 2 mm. tubercles.

Applying this rough quantitation to the three groups gave the results in table 3.

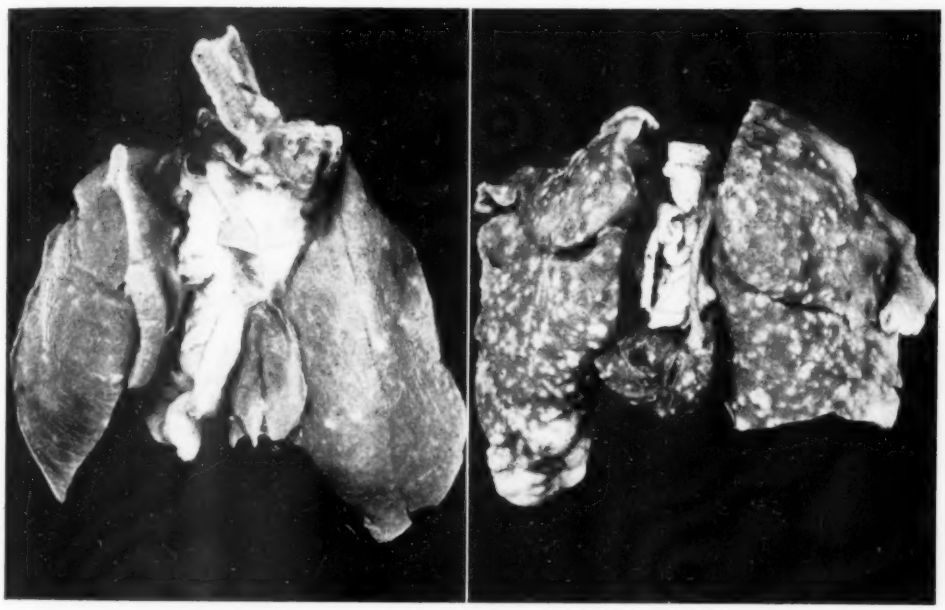

FIG. 2. Rabbit lungs showing the distribution of the tuberculous lesions
(left) Isolated 1 to 2 mm. white tubercles scattered discretely in irregular arrangement. (Grade I)
(right) Uniform, diffuse studding of all lobes with 1 to 2 mm. tubercles. (Grade II)

Extrapulmonary lesions: Tubercles were present in organs other than the lungs in a majority of the animals. The most common site for these extrapulmonary lesions was the kidney, but in several animals there were tubercles present in the appendix, caecum or testes. The distribution of extrapulmonary tuberculosis in the animals of the three groups showed no marked trend in any one group, although a slightly higher number of lesions were present in the animals of group II (tuberculosis and untreated syphilis). Group I showed 9 of 14 animals with these lesions, group II 12 of 13 and group III 9 of 15.

Microscopical sections: Microscopical sections taken from the lesions in the lungs showed evidence of tuberculosis in every animal. There

was variation in the extent of disease present and in some there were evidences of healing. The usual picture was one of isolated tubercles surrounded by areas of partially collapsed lung with intervening areas of normal lung tissue. The tubercles were composed of collections of pale mononuclear leucocytes surrounded by fibroblasts. Multinucleated giant cells were present. In many of the sections the centre of these cell aggregates showed necrosis with loss of cell outlines and deeply and unevenly staining nuclei. In about one-third of the sections central caseation was present. Some of the caseous areas contained scattered calcareous deposits. The lung immediately adjacent to these tubercles showed a distortion of the normal architecture. The interalveolar septa were thickened and tortuous, partly due to the collapsed state of the alveoli, but also due to infiltration of the walls with mononuclear cells. The alveoli in these areas varied greatly in size, some being markedly contracted while others were emphysematous. In a few sec-

TABLE 3

	GRADE I	GRADE II
Group I—Tuberculosis, syphilis, arsphenamine (14 surviving animals)	10 animals	4 animals
Group II—Tuberculosis and syphilis (13 surviving animals)	2 animals	11 animals
Group III—Tuberculosis and arsphenamine (15 surviving animals)	10 animals	5 animals

tions there were definite cavities with inner walls of necrotic tissue surrounded by collars of pale staining mononuclear cells and fibrous tissue. No areas of pneumonia were present.

Sections of the liver of 2 animals from each group were studied for evidence of damage due to the arsphenamine therapy. No abnormalities were found in any of these.

DISCUSSION

Examination of these results shows that the tuberculosis ran a relatively mild course in the animals of all three groups. X-ray shadows, present in a majority of the animals at six weeks, had almost completely disappeared at sixteen weeks. This clearing was uniform throughout all of the groups and there were no instances of progression of the disease according to X-ray in either the treated animals or the controls, yet all animals had grossly demonstrable tuberculosis at autopsy.

The clinical course of the type of tuberculosis used in these experiments has been described by Thomas (15) in 1932 and recently in an extensive investigation by Burke (16). The latter author, studying the effect of this same strain of tubercle bacilli (B1 Saranac Laboratory) in rabbits, has shown that, whereas X-ray shadows are constantly present during the first few months after infection, they may completely disappear between the third and fourth month. Pathological examination of the lungs at this time of negative X-ray findings showed small amounts of tuberculosis to be present. If the animals were not sacrificed they continued to have negative X-ray films for periods as long as eight or nine months, depending somewhat on the infecting dosage. Eventually fresh shadows would appear which would show rapid progression with resultant death of the animal from tuberculosis within a few months of the reappearance of X-ray shadows. Although Burke used the intratracheal route of inoculation, whereas our animals were injected intravenously, and his infecting dosage was not identical with ours, he had a spread of dosage which would include ours.

Thomas (15) pointed out this diphasic character of tuberculosis produced by B1 in rabbits. He found that, of any series of rabbits inoculated, a certain proportion would die relatively early (at about one month) but that the remainder of the animals would develop a chronic form of tuberculosis with a separate mortality peak later on, so that any conclusions drawn from survival times must include the deaths in both phases. The number dying in the first phase and the period between the two phases was determined somewhat by the size of the infecting dose. His animals which died during the first month after inoculation all showed a tuberculous pneumonia, whereas none of our animals which died soon after infection, as described above, showed any pneumonic process.

As has been shown by these investigators, tuberculosis produced in rabbits by the use of small doses of this strain of bacilli (B1) runs a protracted course, with a tendency toward healing at first, but with an eventual spread of the disease resulting in the death of the animal. The development of this latent period of partial healing can be modified or prevented by the use of larger doses of bacilli. Thus, the rabbit's resistance to progression of the tuberculosis at this stage is not an absolute one.

Despite moderately intensive arsphenamine therapy, the course of the tuberculosis produced in our animals followed exactly the clinical

picture described by Thomas and by Burke for the period during which our observations were maintained. There was X-ray evidence of a considerable involvement with tuberculosis in the majority of animals before treatment with arsphenamine was instituted. It is known that the X-ray gives an incomplete picture of the amount of disease actually present in rabbits. Yet, after ten weeks of arsphenamine, the animals were apparently healthy, the X-ray shadows had cleared almost entirely, and the amount of tuberculosis demonstrable at section was much less than that seen by X-ray before therapy. Arsenical therapy did not prevent the healing of a large amount of the tuberculosis present in these animals, and all animals were in the latent phase of the tuberculous infection when the experiment was terminated.

The animals were not followed beyond this period because it was felt that, if arsphenamine were to exert an effect, it should be demonstrable during or shortly after the cessation of its administration. It was also felt that survival times, in such a small group of animals, would not have provided as good an index of the effect of the arsphenamine, as the comparative measurements of the amount of tuberculosis present at autopsy soon after arsenical therapy. However, as the behavior pattern of the disease, as far as it was allowed to go, coincided with that described by other observers, and since all the animals showed foci of active tuberculosis, including a high percentage of extrapulmonary lesions, it would seem reasonable to assume that, had the animals been followed indefinitely, they would have all eventually died of tuberculosis.

There did not seem to be any measurable difference in the amount of tuberculosis present in the two arsphenamine treated groups, one of which was infected with syphilis. The control group of animals, infected with both syphilis and tuberculosis, which received no arsphenamine showed slightly but definitely more tuberculosis at section. Although the groups are small this percentage of variation is statistically significant and would indicate that tuberculosis coexisting with syphilis runs a less benign course when the syphilis is not treated with arsphenamine. However, from our data no conclusions can be drawn as to whether this effect was due to the presence of the syphilis or the absence of the arsphenamine. Since there are such unavoidable chances for error in measuring experimental tuberculosis, such as unconscious selection of animals more heavily infected, or constitutionally less resistant, all into one group, we feel that it is more accurate to conclude that the

tuberculosis in the treated animals fared no worse than in the control group.

The fact that 11 of the 13 untreated syphilitic animals developed clinically demonstrable lesions is of interest because the experiment was carried out during the hot summer months in an animal room which is not air-conditioned. Rabbit syphilis is notoriously hard to maintain during hot weather (17), probably due to the fact that an increase in the normally high body temperature of the animal would not have to be great to kill off or modify the treponemes.

SUMMARY

Two groups of tuberculous rabbits, one syphilitic, one nonsyphilitic, were treated for ten weeks with arsphenamine, while one group of animals with both syphilis and tuberculosis was maintained as a control without treatment. X-ray shadows of tuberculosis were present in the majority (30 of 42) of the animals and almost totally disappeared during the course of treatment in both treated animals and controls. The arsphenamine treatment failed to produce any demonstrable adverse effect on the tuberculosis as judged by estimations of the amount of tuberculosis present at autopsy in the animals of the three groups.

The Wassermann reaction (when performed by the technique described) gave one false doubtful result in the sera of 104 tuberculous animals and was definitely, although only transiently positive eight weeks after infection with syphilis in 15 of 25 animals tested at that time.

SUMARIO

Dos grupos de conejos tuberculosos, uno con sífilis y otro sin ella, fueron tratados con arsfenamina por espacio de diez semanas, a la vez que se retenía sin tratamiento como testigo a un grupo de animales que tenía tanto sífilis como tuberculosis. En la mayoría de los animales (30 de 42) el roentgenograma reveló sombras tuberculosas, pero desaparecieron casi totalmente durante el transcurso del tratamiento tanto en los animales tratados como en los testigos. La arsfenaminoterapia no produjo ningún efecto adverso demostrable sobre la tuberculosis, según pudo apreciarse por los cálculos de la tuberculosis presente en la autopsia en los animales de los tres grupos.

La reacción de Wassermann (verificada con la técnica descrita), acusó un resultado dudoso falso entre los sueros de 104 animales tuberculosos,

en tanto que fué neta positiva, aunque sólo transitoriamente, en 15 de 25 animales comprobados, a las ocho semanas de haberlos infectado con sífilis.

We wish to express our thanks to Miss Jane Haber for technical assistance with the Wassermann reactions.

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THE PERMEABILITY OF FIBROUS TISSUE TO TUBERCLE BACILLI[1]

DIRAN YEGIAN AND HENRY HALLEY, JR.

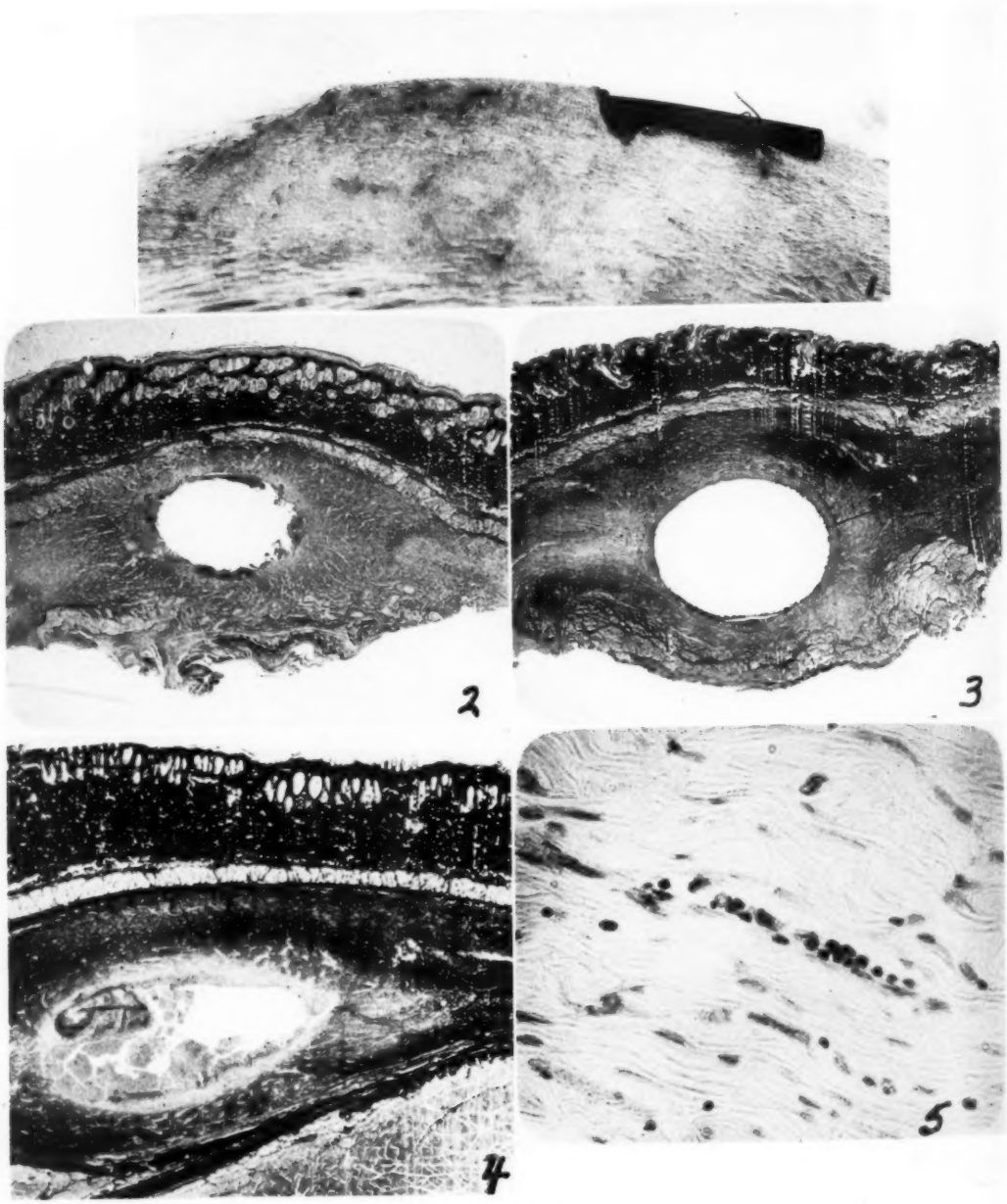
It has been generally assumed that the fibrous capsule of the tubercle prevents the escape of bacilli. However, a close inspection of the residual lesions of pulmonary tuberculosis commonly encountered in subjects dying of other causes, at times discloses minute recent lesions contiguous to the residual ones, suggesting that the recent lesions were produced by the escape of bacilli through the capsule of the older lesions.

These opposing views concerning the permeability of fibrous tissue to the tubercle bacillus apparently are not supported by convincing experimental or pathological evidence. The problem, however, has an important bearing on the pathogenesis of the disease.

The object of the present study was to determine whether fibrous tissue would permit the passage of the tubercle bacillus. In the experiment 61 guinea pigs were used. Thirty-six of these were healthy and nonsensitized; the remaining 25 had been sensitized by a subcutaneous injection into the groin of 1 cc. of a heavy suspension of attenuated tubercle bacilli, strain R1.

Procedure: The interscapular region of the animal was shaved and, under aseptic precautions, a transverse incision about 1 cm. long was made through the skin and subcutaneous tissues. By blunt dissection, these tissues were freed from the underlying structures for a distance of 4 cm. Into the channel thus formed, a rubber tube, 4 mm. in diameter, was inserted. The external end of the tube was sutured with copper wire to the skin 2 cm. from the point of incision (figure 1), thus permitting the mouth of the wound to heal without interference, an important point in the technique. In order to avoid trauma and infection of the wound, each animal was placed in a separate cage. The bedding was sawdust and every endeavor was made to keep the cages scrupulously clean. Yet, in spite of these precautionary measures, the wounds in a few instances became infected, and these animals were excluded from the experiment. The rubber tube was removed after a period of six, thirty

[1] From the New York State Hospital for Incipient Tuberculosis, Ray Brook, New York.



FIGS. 1–5

or sixty days, at which time the wounds were clean and there was no evidence of bleeding. Immediately following the removal of the tube, 0.1 mg. of virulent tubercle bacilli, strain H37, suspended in saline solution was allowed to flow into the channel. The mouth of the channel was plugged with cotton, several layers of gauze were placed over the channel and fixed in position by a wide band of adhesive tape encircling the body of the animal. Ten control animals were smeared with a heavy suspension of tubercle bacilli over the skin in the interscapular region and bandaged in the manner described above. No animal in this group showed evidence of tuberculosis after a period of three months, demonstrating apparently that, with this technique, infection by way of the mouth or through the skin does not occur.

The animals were sacrificed from one to twelve days following the implantation of the tubercle bacilli into the channel. At necropsy, the lymph nodes in the axillae and groins draining the fibrous channel area were removed under sterile conditions and ground in a sterile mortar. Part of the emulsified nodes of each animal was stained for tubercle bacilli and part injected into a healthy guinea pig, which a few days previously had failed to react to an intracutaneous injection of Old Tuberculin. The channel of fibrous tissue was removed with the overlying skin and fixed in 10 per cent formalin. Later the channel of fibrous tissue was divided into from four to eight parts. Paraffin sections were made from each part and stained for tubercle bacilli and for fibrous tissue.

Figure 2 is a stained microscopical section of the wall of a fibrous channel twelve days old, into which tubercle bacilli had been implanted on the sixth day. The inner portion of the wall presents granulation tissue; the outer portion fibrous tissue, as revealed by a connective-tissue stain. Other sections, stained for tubercle bacilli, showed the presence of these microörganisms in all parts of the wall; the larger number appeared in the granulation tissue and were apparently located in the intervascular spaces.

Figure 3 is a stained microscopical preparation of the wall of a fibrous channel thirty-three days old, into which tubercle bacilli had been implanted on the thirtieth day. The fibrous tissue in the wall is more dense and less vascular than in figure 2, and in only a few instances were tubercle bacilli found in the wall.

Figure 4 is a microscopical preparation of the wall of a fibrous channel sixty-three days old, into which tubercle bacilli had been implanted on

the sixtieth day. The wall is comprised of mature fibrous tissue. In a few instances tubercle bacilli were found in the wall.

In table 1 are presented the results in 36 nonsensitized guinea pigs in which a subcutaneous fibrous channel had been produced, varying in age from six to sixty days, previous to the implantation of tubercle bacilli. The animals were sacrificed one to seven days following the implantation of bacilli. The axillary and inguinal lymph nodes draining the experimental field revealed the presence of tubercle bacilli in 34 of the 36 animals, as determined by animal inoculation.

TABLE 1

Thirty-six nonsensitized guinea pigs

Number of animals in each subgroup	5	5	5	12	3	3	3
Age (in days) of fibrous capsules at the time of implantation of the tubercle bacilli	6	30	30	30	30	60	60
Number of days tubercle bacilli were present in the capsule	6	3	4	5	7	1	3
Number of animals positive on lymph node inoculation	5	5	5	11	3	2	3

TABLE 2

Twenty-five sensitized guinea pigs

Number of animals in each subgroup	2	2	3	3	5	7	3
Age (in days) of fibrous capsules at the time of implantation of the tubercle bacilli	30	30	30	30	60	60	60
Number of days tubercle bacilli were present in the capsule	5	7	9	12	1	3	4
Number of animals positive on lymph node inoculation	1	2	3	2	4	6	3

Table 2 presents the results in 25 sensitized guinea pigs. The fibrous channels were thirty or sixty days old when the tubercle bacilli were implanted. The animals were sacrificed one to twelve days following the implantation of tubercle bacilli. The axillary and inguinal lymph nodes draining the experimental field revealed the presence of tubercle bacilli in 21 of the 25 animals, as determined by animal inoculation.

The path of the bacilli through the wall of fibrous tissue has not as yet been determined. However, in one instance, a microscopical section of the subcutaneous tissue lying between the fibrous channel and the adjoining lymph nodes revealed a longitudinal view of a lymph channel

containing only white blood cells and tubercle bacilli (figure 5). This observation would indicate that at least some of the bacilli were conveyed by way of the lymph channels.

The experimental work here recorded justifies the conclusion that tubercle bacilli pass through fibrous tissue which is analagous to the fibrous tissue present in the capsule of the tubercle.

We are indebted to Mr. Joseph M. Kurung for his technical assistance.

CLINICAL AND LABORATORY REPORTS

PULMONARY TUBERCULOSIS WITH GENITO-URINARY TUBERCULOSIS[1]

A Case of Probable Bovine Origin

FRED H. HEISE AND WILLIAM STEENKEN, JR.

Mr. G. W. F., a student, nineteen years of age, from Baltimore, Maryland, entered Trudeau Sanatorium on December 20, 1939. He stated he had last been well November 1, 1939, at which time he had felt toxaemic and had had a pain in his left lower chest, night-sweats, chills, fever and an unproductive cough. By November 18, 1939 his fever had reached 103°F. and his chest pain had become marked. A diagnosis of pleurisy with effusion had been made by physical and X-ray examinations of his chest. On November 26, 1939, 700 cc. of cloudy amber fluid had been removed and an additional 300 cc. two days later. Following the second thoracocentesis his temperature gradually had returned to normal. No tubercle bacilli had been found in the fluid on smear examination. There was no history of exposure to tuberculosis. Tonsillectomy had been performed in 1926 and he had been operated upon for intestinal obstruction in 1936.

Physical examination at Trudeau Sanatorium showed him well developed and well nourished, not acutely or chronically ill, and with no significant abnormalities. Chest examination revealed signs of pleurisy and the X-ray film showed general cloudiness throughout the left thorax and a rather questionable area of mottling along the second interspace trunk on the right. Later, following clearing of the pleuritic cloudiness, a small basal lesion was seen on the left. Total and differential blood counts were not significant. The blood sedimentation rate (Cutler method) was 20 mm. One of 9 concentrated sputum examinations revealed one acid-fast organism. None of three sputum cultures showed any growth of tubercle bacilli. Two cultures from six gastric lavages revealed acid-fast organisms which failed to produce tuberculosis in guinea pigs. The urine, on repeated examinations three weeks after entering the Sanatorium, showed albumen and pus cells (100 per high-power field) and occasional red blood cells. Microscopical examinations of the urine revealed acid-fast organisms which grew on culture media and killed guinea pigs with tuberculosis. The colonies on culture were atypical.

[1] From the Trudeau Sanatorium, Trudeau, New York.

Consultations with a genito-urinary specialist resulted in a diagnosis of left sided tuberculosis of the epididymis and possible renal tuberculosis (pyelogram). Epididymectomy was performed March 15, 1940. Cultures from urine April 5, 1940 showed atypical acid-fast organisms. Albumen disappeared except on one occasion during the next month. Pus cells were reduced to 10 per high-power field except for one specimen, that containing albumen, May 17, 1940.

At no time during residence at the Sanatorium was there any fever or symptoms referable to the genito-urinary tract. On account of vague surface pain over the right upper back upon sitting up, an X-ray examination of the spine was made March 1, 1940. This showed irregularity in density (area of rarefaction) in the anterior superior portion of the body of the third lumbar vertebra which was variously interpreted as tuberculosis, result of fracture and a developmental defect. The last interpretation was made by a competent orthopedist who was collecting data for a paper on the subject. The patient had had many chances for injury while playing football and polo. He was placed in a cast. Subsequent X-ray examination six weeks later revealed no changes in the abnormal structure. The cast was removed without apparent harm and the patient returned to his school studies.

An acid-fast organism was seen in the sputum once. This specimen was not cultured. Acid-fast organisms were grown on culture from each of two gastric lavages and from each of three twenty-four-hour specimens of urine. Those from the gastric lavages did not produce skin hypersensitiveness to tuberculin or cause tuberculosis in guinea pigs. The colony growth had the same lag period as do tubercle bacilli. The colony was somewhat rough and chromogenic. It is possible that this strain might have been an avirulent (Ra) type and was not inoculated in sufficient dose to cause skin hypersensitivity in guinea pigs.

The acid-fast organisms grown from the urine on Steenken and Smith (S & S) medium were small, round, flat colonies with nipple centres (dysgonic, according to the British Royal Commission designation). When inoculated into guinea pigs they caused hypersensitiveness to tuberculin, OT, within two weeks and generalized tuberculosis in six weeks. The primary colonies gave rise to small daughter colonies which grew on the primary lysing colonies. The daughter colonies were raised, rough and cream colored and produced marked tuberculosis in guinea pigs (eugonic Rv colonies).

The original dysgonic Rv dissociate isolated from urine and grown on S and S medium for thirty days was inoculated into rabbits, guinea pigs and chickens. Each of two rabbits received 0.01 mg. intravenously and reacted in the skin to 5 per cent OT in two weeks. Each of two chickens received 1 mg. intravenously and did not react to 5 per cent OT in the skin. Each of two guinea pigs

received 1 mg. subcutaneously and later reacted to 5 per cent OT in the skin. All animals and chickens were killed after sixty days. Neither chicken showed any evidence of tuberculosis. Each rabbit had marked tuberculosis of the lungs and kidneys and each guinea pig generalized tuberculosis.

Cultures from the lungs of the rabbits were grown on S and S medium. The colonies had the appearance of an Rv dysgonic bovine strain.

SUMMARY

Acid-fast organisms isolated from the urine of a patient having tuberculous epididymitis did not have the appearance of a typical human type of bacilli. Morphologically they appeared as a bovine growth (Rv dysgonic). When stained upon a smear, they appeared as short, solid acid-fast rods, quite in accordance with the appearance of bovine or avian bacilli. The results of inoculations into chickens, rabbits and guinea pigs would suggest a bovine strain of moderate virulence.

The patient, in addition to the tuberculous epididymitis, had had pleurisy with effusion from which no tubercle bacilli had been obtained, a slight pulmonary parenchymal lesion with the occurrence of an acid-fast organism of unknown viability in the sputum, and a spinal lesion the aetiology of which was not definitely known.

ACUTE RHEUMATIC FEVER[1]

A Case Occurring in a Patient Receiving Pneumothorax Treatment for Pulmonary Tuberculosis

LOUIS SCHNEIDER

In looking through the literature, I have been unable to find any report of acute rheumatic fever with progressive cardiac involvement occurring in a patient with active pulmonary tuberculosis undergoing pneumothorax therapy. In about 5,000 admissions to the Riverside Hospital, Tuberculosis Division, in the past ten years, no such case has been encountered except the one herein reported. Goldberg in *Clinical Tuberculosis*, Vol. II 1939—K 58, says that it is the general experience that acute articular rheumatism rarely, if ever, occurs in patients having active tuberculosis.

The following case history is extremely interesting in that it reveals a young colored girl with active pulmonary tuberculosis who, while undergoing pneumothorax treatment, developed rheumatic carditis, and although her heart has been badly damaged by the rheumatic infection, the tuberculous process has thus far been under complete control by pneumothorax therapy, more than a year after the onset of her pulmonary disease and some eight months after the subsidence of the rheumatic infection.

J. J. was a sixteen year old Negro schoolgirl when first admitted to Bellevue Hospital on October 3, 1939 with complaints of weakness, cough productive of one cup of yellow sputum daily, easy fatigue and loss of 11 pounds during the preceding two months. Four years previously, she had developed a painless swelling in the right submaxillary region which slowly subsided under ultraviolet radiation; a small discharging sinus appeared in this area two years ago, and the submaxillary glands have been becoming larger and have been accompanied by a chain of firm, painless nodes in the right anterior cervical region.

Family history: Her father had been ill with pulmonary tuberculosis at least three years, but his case cannot be traced. Her past history is essentially negative, except for adenopathy above described.

Findings at Bellevue Hospital were:

1: Thin young Negress appearing chronically ill.

[1] From the Tuberculosis Division, Riverside Hospital, Dr. Max Taschman, Director, New York, New York.

2: Many carious teeth.
3: Firm, moderately enlarged, non-tender nodes in right submaxillary area and in both anterior cervical regions.
4: Heart negative for any abnormalities.
5: Lungs: Right, clear.
Left, dull to second anterior rib and fourth thoracic vertebra; medium coarse râles and few consonating râles left upper lung field.
6: Abdomen negative.
Nothing else of note on examination.

An X-ray film taken October 11, 1939 at Bellevue showed a soft homogeneous density from above the clavicle to the third anterior rib on the left side; there was an irregular highlight in the first interspace and scattered infiltrations in the third and fourth interspaces on that side. Her sputum was positive on admission. Sedimentation rate was 30 mm. per hour. Red cells, 4,540,000; haemoglobin, 80 per cent; white cells, 7,600; polynuclears, 49, lymphocytes, 43, monocytes, 5, eosinophils, 2, basophils, 1.

Patient ran a low grade temperature. Pneumothorax was started on the left side on October 18, 1939 and after four refills, producing a selective 25 per cent collapse of the left lung, she was transferred to Riverside Hospital. Her weight had remained stationary.

She was admitted to Riverside December 29, 1939 and at this writing she is still there. Upon admission, her general condition was good, her respiratory symptoms had practically subsided; she had a small draining sinus in the right submaxillary region. In addition to ultraviolet therapy to her cervical nodes given about twice weekly, she continued to receive pneumothorax treatment on the left side once or twice weekly. Only one positive sputum was obtained on October 26, 1939, but since then and to the present time repeated concentrations have been negative. An X-ray film of October 25, 1939 (figure 1) showed 35 per cent selective collapse of the diseased upper lobe, the remainder of the lung fields being clear. For the first two weeks of her stay the temperature hovered around 100°F. and then remained about normal until the rheumatic episode began.

Her course continued satisfactorily, when on January 29, 1940 she began to run a high intermittent temperature which showed fluctuations between 103° and 104°F. At the same time she complained of sharp pains in all the large joints of the upper and lower extremities. Examination of February 1, 1940 revealed limitation of motion, swelling and tenderness of the large joints of the upper and lower extremities, especially the wrists and knees. The heart sounds were reported distant, and there was a distinct systolic murmur at the apex; in addition there was a suggestion of a gallop rhythm. A rash of the *erythema multiforme* type covered the chest and the abdomen. From the above findings a diagnosis of acute rheumatic fever was made by the resident,

Doctor Liebowitz. An EKG on February 8, 1940 revealed low voltage in all QRS complexes, depressed T waves and first-stage conduction block with PR interval of 0.25 sec. A diagnosis of acute rheumatic myocarditis with serious myocardial damage was made by Dr. J. Burstein. After a few days on large doses of salicylates without response, she began to receive an average of 10 grains of pyramidon every six hours on February 13, 1940; this drug was continued until April 3, 1940 when the rheumatic attack showed evidence of subsiding.

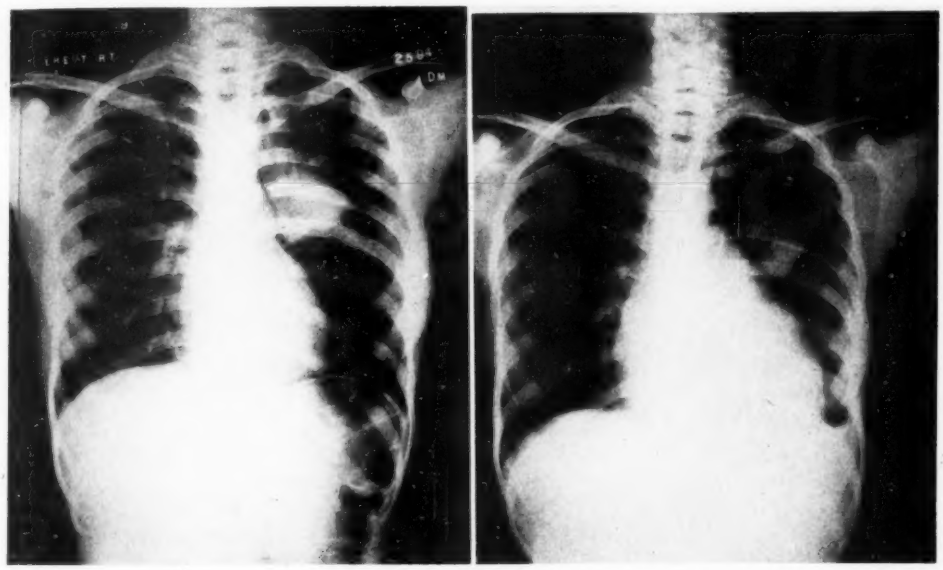


FIG. 1. (Left.) Left therapeutic pneumothorax, normal heart
FIG. 2. (Right.) Good selective collapse, mitral heart

She ran a high temperature during the first five weeks of her rheumatic infection, and then a low grade fever, temperature fluctuating between 99° and 100.5°F. for six more weeks after which time her temperature returned to normal and has remained normal to this day.

Blood counts showed a leucocytosis of from 21,000 to 25,000 during the first four weeks of the rheumatic episode; a slight leucocytosis persisted for two months thereafter. It is interesting to note that she never manifested any appreciable anaemia.

On April 3, 1940 another EKG still showed slightly prolonged PR interval; the systolic murmur at the apex was quite pronounced at this time and the blood pressure was 108 over 60. On April 15, 1940 an X-ray film revealed a

typical mitral heart, and there was a presystolic and systolic murmur at the apex transmitted to the midaxillary line. In the film of June 6, 1940 (figure 2) is seen a distinctly mitral heart, which had become quite enlarged, as compared to the heart shadow on the first film.

It was deemed necessary during her attack of acute rheumatic fever to continue a minimum of pneumothorax treatments; she received 200 cc. of air on February 13, March 5 and April 5, 1940, ending in negative pressures. She took these treatments without much trouble.

At present, the patient is quite comfortable and has no respiratory complaints. She is allowed bathroom and diningroom privileges, but is otherwise confined to bed. Since the middle of April, 1940 her temperature has been practically flat though her pulse races a little at times. She continues to receive about two pneumothorax refills monthly, has a good collapse of the left lung and has developed some serous fluid on the left side which is negative for tubercle bacilli. Her sputum continues negative. A basal metabolic rate done on May 8, 1940 was −3 per cent. On admission to Riverside she weighed 107 pounds. Her weight fell to 98 pounds at the end of her rheumatic attack early in April, but since then she has steadily regained so that she weighed 126 pounds on December 1, 1940. Her cervical nodes have become smaller, and the sinus in her right submaxillary region became closed on September 16, 1940 whereupon ultraviolet treatment to this region was discontinued. Previously, an aspiration biopsy of the right upper cervical nodes was positive for tubercle bacilli on guinea pig inoculation.

CONCLUSION

A patient is reported who developed acute rheumatic fever with rapid, severe, non-fatal cardiac damage while undergoing pneumothorax treatment for pulmonary tuberculosis. Collapse therapy was continued cautiously during the patient's highly febrile rheumatic infection of many weeks' duration, and her tuberculosis has remained under control despite the apparent intense rheumatic cardiac involvement.

TUBERCULOSIS OF THE SKULL[1]

JASON E. FARBER AND WILLIAM F. BESWICK

During the past year we have had opportunity to observe a patient with tuberculosis of the skull and have found another such case in our files. The two cases make the subject of this report.

CASE REPORTS

Case 1: C. C., a mentally retarded Negro housewife, aged forty-eight, was admitted to the Meyer Memorial Hospital on July 8, 1940 complaining of a tumor mass and pain over the left fronto-parietal area of the head. The lesion was noticed by the patient two months previously. At first it had felt firm and tender but later as it enlarged it felt softer and less painful.

During 1935 the patient had attended the hospital clinics for iritis of the left eye. Her Wassermann test was positive and several courses of arsenic and bismuth were given.

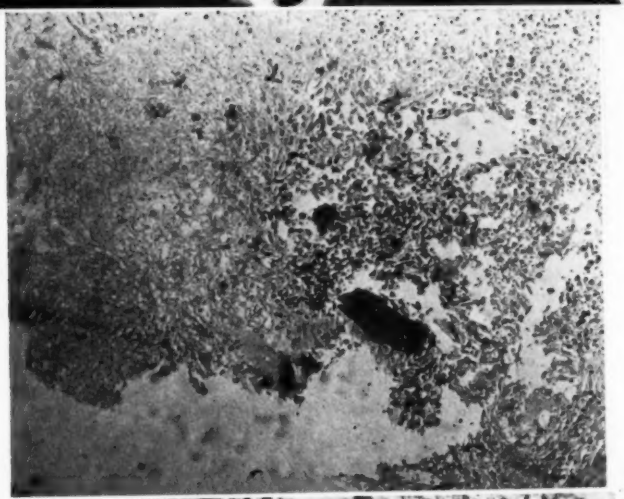
The patient was a well developed, well nourished Negro woman of forty-eight years who did not appear acutely ill. There was a soft fluctuating mass, 4 cm. by 8 cm. by 3 cm., in the left fronto-parietal area of the scalp. A scar was seen on the cornea of the left eye. Physical and neurological examinations were otherwise negative.

The patient ran a daily low grade fever. Aspiration of the mass revealed a yellow green purulent material containing white fibrinous particles. Approximately 50 cc. of exudate was obtained by incision of the lesion. The surrounding galea appeared oedematous and the underlying bone felt rough to needle palpation.

Roentgenograms of the skull showed an area of destruction in the left parietal bone encroaching upon the coronal suture and measuring 1.5 cm. by 2 cm. in the outer table and 3 cm. by 4 cm. in the inner table (figure 1). Encephalograms were negative. A roentgenogram of the chest and the sputum were both negative. The blood count showed a hypochromic normocytic anaemia. The Wassermann and Kahn tests were positive.

On July 15, 1940 a small scalp flap was turned down and dissected from the pericranium. Near the centre of the flap a well circumscribed abscess was

[1] From the Tuberculosis and Neurological Services of the Edward J. Meyer Memorial Hospital and the University of Buffalo Medical School, Buffalo. New York.



FIGS. 1–3

encountered and approximately 50 cc. of a greenish watery fluid escaped. The cavity wall was yellow green and of cheesy consistency. The galea and pericranium were destroyed over an area of 3 cm. There was a defect in the outer table of the skull approximately 1.5 cm. in diameter. The surrounding bone was removed with a rongeur until normal bone was encountered. On the surface of the dura grayish-pink fleshy granulations, roughly 1 cm. thick, were found and partially removed by curettement. Further removal was not accomplished in order to avoid tearing of the dura. Two rubber tissue drains were left within the wound protruding from both limbs of the incision. Through these, daily irrigations were made with Dakin's solution. The drains were shortened 1 cm. each day. The wound healed by primary intention.

Surgical material, consisting of specimens from (*1*) the abscess wall, (*2*) the parietal bone and (*3*) dural granulations, showed a tuberculous type of granulation tissue with giant cells of the Langhans' type, areas of caseation, epithelioid cells and tubercles. Destruction of the bone by the ulcerative tuberculous process was evident. Sections showed small fragments of bone surrounded by granulation tissue and caseation as seen in figure 2. Stains for tubercle bacilli were negative. However, a guinea pig injected with material from the lesion on July 17, 1940 showed tuberculosis at autopsy on September 6, 1940.

Soon after the surgical exploration was made the patient complained of pain in the right hip, and swelling in the right groin was noted. A roentgenogram showed the joint space of the right hip almost completely obliterated and hazy in appearance. The articulating acetabulum and the head of the femur showed irregular areas of decreased density. On aspiration of the right hip a cream colored purulent fluid was obtained and from this tubercle bacilli were grown. A guinea pig injected with the exudate showed tuberculosis at autopsy. Roentgenograms of the dorsal and lumbar spine were negative. At the present time the patient is running a fairly stable clinical course and is receiving treatment for the tuberculosis of the hip.

Case 2: The patient, a twenty-five year old white man with advanced pulmonary tuberculosis, was admitted to the Meyer Memorial Hospital in April, 1931. He complained of severe constant occipital headaches, blurred vision, spells of vomiting and inability to stand. Examination showed signs of advanced pulmonary tuberculosis associated with those of meningeal irritation

FIG. 1. (Top.) Case 1. Roentgenogram of the skull, lateral view, showing area of bony destruction.

FIG. 2. (Center.) Case 1. Microphotograph of the lesion in the skull showing fragments of bone, caseation, tuberculous granulation tissue and cellular infiltrate.

FIG. 3. (Bottom.) Case 2. Microphotograph of the lesion in the skull showing bony trabeculae, granulation tissue and cellular infiltrate.

but no clear-cut localizing neurological signs. The pressure and cell counts of the cerebrospinal fluid were normal. Ventriculography was resorted to but no localized lesion was identified. The patient expired one year later. At autopsy (Dr. W. F. Jacobs), a tuberculoma was found in the left cerebellar hemisphere. There was a path of direct extension of the tuberculous process to the occipital bone. The inner and outer tables of the skull were eroded over an area 1 cm. in diameter. Microscopical study of the bone (figure 3) showed areas of caseation, round cell and epithelioid cell infiltration, tuberculous granulation tissue and spicules of devitalized bone. No other bone lesions were found.

DISCUSSION

In both cases reported there was definite destruction of the bone of the skull by a tuberculous process. Histologically, the osseous lesions were similar and showed typical caries of the bone with tuberculous granulation tissue, caseation and a cellular infiltrate consisting of round, epithelioid and giant cells. Pathogenetically, the two lesions differed somewhat. In the first patient, the bone involvement was obviously haematogenous in origin; the lesions of the eye and hip conform to the picture. In the second instance, the skull was apparently involved by contiguity, by extension of an underlying expanding tuberculous process of the brain to the overlying bone. As previously noted, the second case was entirely unsuspected, an accidental finding at autopsy. There was no overlying lesion of the scalp.

SUMMARY

Two cases of tuberculosis of the skull are presented. In the first case the bone involvement is undoubtedly a blood-borne infection. In the second, the skull is apparently involved by contiguity from an underlying tuberculoma of the cerebellum and was an accidental finding at autopsy. Histologically, both lesions show typical osseous tuberculosis.

SUMARIO

Preséntanse dos casos de tuberculosis craneal. En el primero la invasión ósea representó sin duda una infección hematógena. En el segundo se afectó aparentemente el cráneo por contigüidad de un tuberculoma subyacente del cerebelo, y el dato fué un hallazgo fortuito en la autopsia. Histológicamente, ambas lesiones revelaban típica tuberculosis caseosa.

We are indebted to Dr. William F. Jacobs for the microphotographs.

GROWTH AND VIRULENCE OF TUBERCLE BACILLI[1]

A Study of the Effect of Vitamins B_1 and B_6, Riboflavin, Colchicine, Phthiocol and Thyloquinone

FRED H. HEISE AND WILLIAM STEENKEN, JR.

Prompted by the published reports of the growth stimulating properties of vitamin B_1 upon plant life and the development of new varieties by exposure of seeds to colchicine and other substances, it was thought interesting to study the effect of some of these substances upon the tubercle bacillus.

The virulence and morphology of H37 Ra (avirulent) and H37 Rv (virulent) dissociates have remained constant for five years when grown upon a modified P and B medium of pH 7.2. For this reason the type H37 tubercle bacillus was chosen.

Twenty cc. of the modified P and B medium was placed in each of 50 cc. Erlenmeyer flasks and to these were added seperately concentrations of 1:1000 and 1:100,000 of vitamins B_1, B_6, riboflavin and also colchicine.[2] All the prepared flasks were autoclaved at 10 pounds pressure for ten minutes. The riboflavin recrystallized on cooling.

Two flasks of each of the substances studied and of each concentration were seeded with a 2 x 2 mm. pellicle of H37 Ra and Rv tubercle bacilli. The growths were transferred serially to the same medium at ten-day intervals for eighty days. At the same time seeding and transfers were carried on in like manner on the same medium without the substances to be tested. No marked stimulation or inhibition of growth was noticed in any of the test flasks as compared to the controls. Neither did the microscopical morphology of the tubercle bacillus change. Transplants to a solid medium (Steenken and Smith) revealed no change in morphology or rate of growth over the controls.

A mixture of B_1, B_6, riboflavin and colchicine in concentrations of 1:1000 and 1:100,000 was seeded in P and B medium with the dissociated H37 as before. No change in rate of growth or morphology could be detected.

The naphthaquinones were weighed in 10 mg. lots and dissolved in 100 cc. of 10 per cent glycerine in distilled water. The diluent was slightly below the boiling point at the time of addition of the naphthaquinones to facilitate solution. The solutions were sterilized in the autoclave at 10 pounds pressure for twenty minutes and then allowed to stand in the ice-box for twenty-four hours.

[1] From the Trudeau Sanatorium, Trudeau, New York.

[2] These substances were kindly furnished by Merck & Company.

Concentrations of these solutions were added to modified P and B medium as follows: 0.05, 1.0, 2.0, 3.0, 4.0 and 5.0 mg. per cent. The flasks were then seeded with ten-day-old viable cultures of H37 Ra and Rv variants. These were incubated at 37.5°C. together with control cultures. At the end of six days definite inhibition of growth of the Rv variant was seen in all of the flasks containing thyloquinone. No growth was visible in concentrations of 4.0 or more mg. per cent. Very slight inhibition of growth was noted in the flasks containing phthiocol of less than 5.0 mg. per cent in that the pellicle was diffusely scattered and veil-like. In the 5.0 mg. per cent concentration no growth could be noted.

The Ra variant showed inhibition of growth at the end of twelve days in the flasks containing thyloquinone and slight inhibition in those with phthiocol. Both Ra and Rv variants grown on these substances had a definite pigmented appearance which disappeared when transplanted to other media. It is possible that the colored solutions had adhered to the organisms.

The virulence of the H37 variants after growing on the various substances mentioned above was tested by inoculating 30 male albino (tuberculin skin insensitive, 5 per cent OT) guinea pigs of about 300 g. each. All animals including controls reacted to tuberculin skin tests three weeks after inoculation. All guinea pigs inoculated with the Rv dissociate died of generalized tuberculosis within two months. Those inoculated with Ra variant lived three months at which time they were killed and at autopsy none showed progressive tuberculosis. Only occasionally there was seen a small caseous focus at the site of inoculation. Thus no change in virulence was detected.

SUMMARY

No inhibition or stimulation of growth of H37 tubercle bacillus variants Ra and Rv, nor change in virulence could be detected by additions of various concentrations of vitamins B_1, B_6, riboflavin and colchicine to modified P and B medium.

Definite inhibition, partial or complete, without change of virulence could be noted when these tubercle bacilli variants were grown on some concentrations of thyloquinone and phthiocol.